A STUDY OF EXPRESSION OF THYROID TRANSCRIPTION FACTOR (TTF-1) IN ENDOMETRIAL ADENOCARCINOMA OF UTERINE CORPUS

Dissertation submitted in

partial fulfilment of the requirements for the degree of

M.D. (PATHOLOGY)

BRANCH - III

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MADRAS MEDICAL COLLEGE

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THE TAMIL NADU

DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

APRIL 2016

CERTIFICATE

This is to certify that this Dissertation entitled **"A STUDY OF EXPRESSION OF THYROID TRANSCRIPTION FACTOR(TTF-1) IN ENDOMETRIAL ADENOCARCINOMA OF UTERINE CORPUS"** is the bonafide original work of **Dr. BRINDA. M**, in partial fulfillment of the requirement for M.D., (Branch III) in Pathology examination of the Tamilnadu Dr.M.G.R Medical University to be held in April 2016.

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DECLARATION

I, **Dr.Brinda.M,** solemnly declare that the dissertation titled **"A STUDY OF EXPRESSION OF THYROID TRANSCRIPTION FACTOR(TTF-1) IN ENDOMETRIAL ADENOCARCINOMA OF UTERINE CORPUS"** is the bonafide work done by me at the Institute of pathology, Madras Medical College under the expert guidance and supervision of **Prof. Dr.M.P.KANCHANA,** M.D., Professor of Pathology, Institute of obstetrics and gynaecology, Madras Medical College. The dissertation is submitted to the Tamilnadu Dr. M.G.R Medical University towards partial fulfillment of requirement for the award of M.D., Degree (Branch III) in Pathology.

Place: Chennai

Date: **Dr. BRINDA .M**

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INSTITUTIONAL ETHICS COMMITTEE
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CERTIFICATE OF APPROVAL

To
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Dear Dr.M.Brinda,

The Institutional Ethics Committee has considered your request and approved your study titled **"A study of expression of Thyroid Transcription Factor (TTF-1) in Endometrial adenocarcinoma of uterine corpus". No.04102014.**

The following members of Ethics Committee were present in the meeting held on 07.10.2014 conducted at Madras Medical College, Chennai-3.

1.	Dr.C.Rajendran, M.D.,	: Chairperson
2.	Dr.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
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9.	Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
10.	Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

MEMBER SECRETARY
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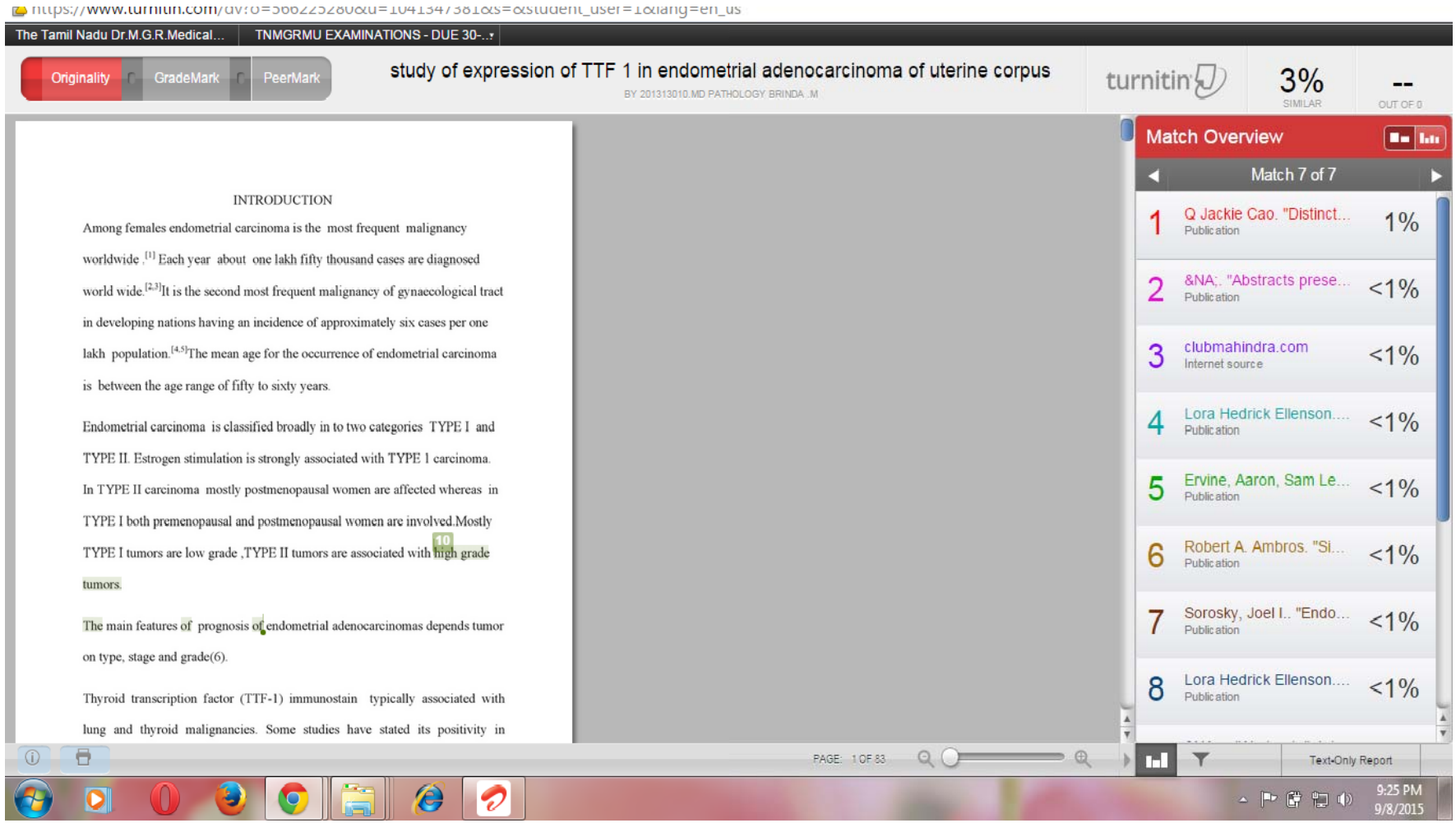
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INTRODUCTION
Among females endometrial carcinoma is the most frequent malignancy worldwide .[1] Each year about one lakh fifty thousand cases are diagnosed world wide.[2,3]It is the second most frequent malignancy of gynaecological tract in developing nations having an incidence of approximately six cases per one lakh population.[4,5]The mean age for the occurrence of endometrial carcinoma is between the age range of fifty to sixty years.
Endometrial carcinoma is classified broadly in to two categories TYPE I and TYPE II. Estrogen stimulation is strongly associated with TYPE 1 carcinoma. In TYPE II carcinoma mostly postmenopausal women are affected whereas in TYPE I both premenopausal and postmenopausal women are involved.Mostly TYPE I tumors are low grade ,TYPE II tumors are associated with high grade tumors.
The main features of prognosis of endometrial adenocarcinomas depends tumor on type, stage and grade(6).
Thyroid transcription factor (TTF-1) immunostain typically associated with lung and thyroid malignancies. Some studies have stated its positivity in
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The main features of prognosis of endometrial adenocarcinomas depends tumor on type, stage and grade[6]

Thyroid transcription factor (TTF-1) immunostain is typically associated with lung and thyroid malignancies. Some studies have stated its positivity in endometrial carcinomas also in ovarian and cervical carcinomas[8,9,10]

Thyroid transcription factor is a Deoxy ribonuclease protein determined by the gene placed on chromosome 14q13.It has been regarded as a specific and sensitive marker for tumors arising in thyroid and lung[10]

1

ABBREVIATIONS

TTF-1	:	Thyroid Transcription Factor-1
WHO	:	World Health Organisation
PCOD	:	Polycystic ovarian disease
MMMT	:	Malignant mixed mullerian tumour
IHC	:	Immunohistochemistry
H & E	:	Hematoxylin & Eosin
EIN	:	Endometrial intraepithelial neoplasia
FIGO	:	International Federation of Gynaecology and Obstetrics
EGFR	:	Epidermal growth factor receptor
EIC	:	Endometrial intraepithelial carcinoma
ISOGP	:	International Society of Gynecological Pathologists

CONTENTS

ABSTRACT

Among females endometrial carcinoma is the most frequent malignancy worldwide . It is the second most frequent malignancy of gynecological tract in developing nations having an incidence of approximately six cases per one lakh population. Thyroid transcription factor is a Deoxy ribonuclease protein determined by the gene placed on chromosome 14q13.It has been regarded as a specific and sensitive marker for tumors arising in thyroid and lung. This study is undertaken to probe Thyroid transcription factor positivity in primary uterine endometrial adenocarcinoma and also in malignant mixed mullerian tumour .

AIMS AND OBJECTIVES:

To study the incidence and distribution of Thyroid transcription factor in endometrial adenocarcinoma. To correlate the percentage of expression of TTF-1 with the grade of endometrial adenocarcinoma .And to assess the prognosis based on the expression of TTF-1 for the patients who were on follow up.

MATERIALS AND METHODS:

93 cases Paraffin sections of hysterectomy specimens diagnosed as Endometrial carcinoma will be subjected to routine H&Estaining and IHC marker TTF1 was done for 50 random cases.

RESULTS:

Among 50 randomly selected cases TTF 1 marker was done ,only 3 cases showed positivity for TTF 1. Two cases of moderately differentiated endometrioid carcinoma were focally positive and one case of poorly

differentiated carcinoma was diffusely positive for TTF 1 ,all others were negative.The relationship between TTF 1 positivity and grade of endometrioid carcinoma has a pvalue of 0.004 which is statistically significant.

CONCLUSION:

In our study the incidence of different types of endometrial carcinoma in the 5 years from January 2010 to December 2014 in the Institute of Obstetrics and Gynecology, Madras Medical College ,Chennai was studied. This study confirms that TTF 1 positivity correlates with grade of endometrial carcinoma. Out of the 3 positive cases ,the follow up for 7 months was available for only case of stage I low grade endometrioid carcinoma and the comment on prognosis can only be made on long term followup.

Keywords: Endometrial adenocarcinoma,Thyroid transcription factor

INTRODUCTION

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The main features of prognosis of endometrial adenocarcinomas depends tumor on type, stage and grade[6].

Thyroid transcription factor (TTF-1) immunostain is typically associated with lung and thyroid malignancies. Some studies have stated its positivity in endometrial carcinomas ,also in ovarian and cervical carcinomas[6,7,8].

Thyroid transcription factor is a Deoxy ribonuclease protein determined by the gene placed on chromosome 14q13.It has been regarded as a specific and sensitive marker for tumors arising in thyroid and lung[6].

In recent times TTF-1 positivity has been found in other carcinomas of gynecologic origin including ovary,endometrium and uterine cervix [6,7,8].

This study is undertaken to probe Thyroid transcription factor positivity in primary uterine endometrial adenocarcinoma and also in malignant mixed mullerian tumour .

AIMS

AND

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1) To study the incidence and distribution of Thyroid transcription factor in endometrial adenocarcinoma.

2) To correlate the percentage of expression of TTF-1 with the grade of endometrial adenocarcinoma.

3) To assess the prognosis based on the expression of TTF-1 for the patients who were on follow up.

REVIEW

OF

LITERATURE

REVIEW OF LITERATURE

Embryology and Anatomy:

Endometrium and myometrium are created by union of mullerian ducts between eighth and ninth postovulatory weeks. They are of mesodermal in origin.

At about 20^{th} gestational week ,the surface epithelium invaginates in to the stroma to form glandular structures.

In the prepubertal years ,endometrium is not active. But during reproductive years the endometrium undergoes cyclic morphologic changes.

The uterus of a nulliparous women is pear shaped, hollow measuring around seven to eight centimetre along its long axis and weighs about 40 to 80 grams. Whereas multigravid uterus is larger in weight and it's length varies with increasing parity.

Uterine corpus is triangular in shape. It's divided in to three parts the fundus, body and isthumus. It is lined by endometrial mucosa, which consists of inner layer of endometrium and thick muscular myometrium.

Endometrial mucosa consists of endometrial glands and stroma. It can be divided into basal reserve layer and the superficial functional layer.

ENDOMETRIAL CARCINOMA

Epidemiology and Incidence:

Endometrial carcinoma is the frequent malignancy of female genital system. Its incidence is high in developed nations[9],being 4th common carcinoma in females[1].

Approximately 2 lakh eighty thousand new cases are diagnosed each year worldwide. Accounts for seven percent of invasive cancer in women.

Most cases over 90 percent occur in females elder than 50 years of age. Occurrence most common in menopausal women [1], but it can be found at any age.

Generally endometrial carcinoma produces symptoms by which it can be diagnosed at an early stage. The five year survival rate is higher in developed countries when compared to developing or underdeveloped nations[10,11].

About two percent of all cancer mortality in women is due to endometrial carcinoma[12].

Pathogenesis:

Endometrial cancer can be classified in to 2 categories based upon clinicopathological and molecular genetic features as

1) Type I
2) Type II

Type I :

It is the most common subtype, eighty percent occurs due to excess estrogen stimulation. It develops in the background of endometrial hyperplasia. But it can also arise denovo[13,14,15,16].

They are well differentiated and they closely resemble proliferative endometrial glands, so they are referred as Endometrioid carcinoma.

Women at risk are generally,

- Obese
- Hypertensive
- Diabetic
- Nulliparous /infertility
- PCOD/stein leventhal syndrome
- Tamoxifen treated breast cancer patients
- Ovarian tumors – granulosa cell tumors and thecomas [17,18,19].
- Dysfunctional uterine bleeding patients on estrogen therapy

The tumors under this category are not so aggressive. The carcinomas included under it are endometrioid carcinoma grade one and grade two.[20]

Britton LA et al studies have shown increased estrogen levels in the serum of patients having endometrial cancer[21,22].

Type II:

This type is not associated with hormones and also hyperplasia[23].

Serous type carcinoma the most common type in this category. Other histological type included in this category is clear cell carcinoma, MMMT, undifferentiated carcinoma.

It is not associated with estrogenic influence. Endometrial atrophy is usually associated with it. They are poorly differentiated tumors accounting for 15 percent of cases .

The tumors are serous, clear cell type, MMMT, grade 3 endometrioid and undifferentiated carcinoma.[20]

Etiology:

1) **Age:**

   The risk of endometrial carcinoma increases with advancing age[24].

   Incidence is high in women who are postmenopausal usually the age range is between fifty five to sixty years. Incidence of endometrial carcinoma is unusual in women aged less than forty years.

2) Hormonal stimulation:

Current studies have found that unopposed estrogen therapy is associated with increased risk endometrial carcinoma[25,28,29].

Breast cancer Patients on long term treatment with tamoxifen have an increased risk up to six to eight fold of development of endometrial carcinoma .[26,27]

Women with excess endogenous estrogen exposure like

- Early menarche
- Late menopause
- Tamoxifen therapy ,
- Nulliparous
- PCOD
- Infertility due anovulation are at increased risk[26,27].

3) Constitutional factors:

Obesity is a well defined risk factor for development of endometrial carcinoma[31].It is due augmented availability of peripheral estrogens converting into androgens[30].

Other risk factor is Diabetes [21,2,3].

4)Irradiation:

Endometrial carcinoma mainly serous type has an association with pelvic irradiation ,but whether it's spontaneous or radiation induced is not clear[32,37,39].

5)Diet:

Increase in total calorie intake along with decreased physical activity is associated with elevated risk .

6)Hereditary :

About 10 percent of endometrial cancers are hereditary while most are sporadic.

HNPCC patients have elevated risk [33,34].They manifest with endometrial carcinoma at an younger age, majority of which are high grade non endometrioid carcinomas[35].

McCarty et al stated that individuals with gonadal dysgenesis like Turnor's syndrome have a propensity to develop well differentiated endometrial adenocarcinoma. Out of thirteen cases that were studied ,eleven cases had received estrogen therapy for protracted duration[36].

So whether Turner phenotype or unopposed estrogen therapy for causation of endometrial adenocarcinoma is vague.

Other syndromes associated with endometrial carcinoma are

- **Lynch syndrome**:

Its due to defective DNA mismatch repair genes-MLH 1, MSH6 , MSH2,PMS2. The inheritance pattern is of autosomal dominant type. Most HNPCC tumors are of endometrioid type but other type like serous,clear cell, MMMT and undifferentiated tumors also occur in this group[38].

Immunohistochemical studies with MLH1 and MSH2 antibodies have a sensitivity rate of about sixty nine percent and specificity of hundred percent[40].

- **Cowden syndrome**:

Caused due to mutations in PTEN tumor suppressor gene. It is an autosomal dominant disorder. Patients have an increased risk of breast, endometrium and thyroid malignancies.The risk of endometrial carcinoma varies between 5 to 10 percent compared to 2.6 percent risk in general population.

According to **Nelen MR et al** the histologic type has not been found[41].

MOLECULAR GENETICS:

ENDOMETRIOID CARCINOMA:

Development of Endometrial carcinoma involves acquisition of several genetic alterations in tumor suppressor and oncogenes .The most common altered gene is the PTEN (30-54%) of cases[42].

Genomic sequencing of Type I endometrioid carcinoma have shown that most common mutations are those that increase the signaling through PI3/AKT pathway.AKT is abnormal in cancer pathogenesis.

The association of PTEN change in atypical and nonatypical hyperplasia is approximately 20 – 48 percent [43,44],which supports the view that atypical hyperplasia is the predecessor to carcinoma .

Oncogene PIK3CA mutations are present in about 39 percent of carcinoma, also in all tumor grades[45]. Thus the roles of PTEN and PIK3CA mutations in endometriod carcinoma are different , the former helps for endometrial hyperplasia development , while the latter has a role in conversion of complex atypical hyperplasia to cancer.

P53:

P53 mutations are found in 10 percent of all endometrioid carcinoma most common in grade 3 tumor, intermittedly in grade 2 tumors.

They are not identified in grade 1 tumors which suggests that they have a role in progression, but not in initiation of endometrioid carcinoma[46].

MICROSATELLITE INSTABILITY:

Found in women with HNPCC syndrome in which the most common non colorectal malignancy is endometrial carcinoma[47].

Occurrence of microsatellite instability is approximately 20 percent in sporadic endometrial cancers ,seen also in atypical hyperplasia that are associated with cancer. Most common mutated gene in sporadic microsatellite instability is MLH1 gene[48,49,50].

KRAS :

Studies indicate that K-RAS mutations are seen in 10 – 30 percent of endometrial cancer[51,52,53].It has been identified in all grades of endometrioid carcinoma and also in complex atypical hyperplasia.

Overexpression of EGFR,HER2NEU,BCL2 ,FGFR2,CTNNB1 have been identified[54,55,56].

SEROUS CARCINOMA:

More than ninety percent of cases show P53 mutation [57,58]. About 75 percent of Endometrial intra epithelial neoplasia – precursor lesion for serous carcinoma have P53 mutations[58].

Fifteen percent of these tumors have PIK3CA mutations suggesting role of PI3K/PTEN/AKT pathway in these tumors[59].

In serous carcinoma P53 mutations has early incidence, in contrast to endometrioid carcinoma in which poorly differentiated endometrioid carcinoma, which has aggressive behavior of these tumors[60].

To sum up molecular studies of two types of endometrial carcinomas indicate that these tumors often develop from precursors with addition of genetic alterations.

In serous carcinoma P53 mutations is associated with the alteration of atrophic endometrium to serous intraepithelial carcinoma which on further genetic alterations leads to invasive malignancy.

PRECURSOR LESIONS TO ENDOMETRIAL CARCINOMA:

Endometrial hyperplasia is the precursor lesion for development of endometrioid carcinoma.

It is associated with prolonged estrogenic stimulation of endometrial stimulation, which can be due obesity, nulliparity, exogenous estrogen.

Classification :

Classification proposed by WHO proposed by kurman and Norris [61].

Four categories :

- Simple hyperplasia without atypia
- Complex hyperplasia without atypia
- Simple hyperplasia with atypia
- Complex hyperplasia with atypia

But current WHO classification clubs these four types in to two major categories

- Non atypical hyperplasia
- Atypical hyperplasia[EIN].

Clinical features:

Women usually present with irregular bleeding or found incidentally in biopsy workup done for infertility cases. The bleeding is profuse in women with endometrial hyperplasia or endometrial carcinoma when compared to spotty bleeding in atrophic endometrium.

Gross features:

It may have a velvety or a spongy appearance . Although diffuse endometrial thickening is common, a polypoidal appearance is also noted.

Histological pattern is considered as a prerequisite for diagnosis of endometrial hyperplasia.

NON ATYPICAL HYPERPLASIA:

Characterized by abnormal architechtural patterns with increased gland to stroma ratio.

Simple hyperplasia without atypia:

The stroma is abundant with cystic dilatations of endometrial glands. Cells are stratified ,with columnar morphology and amphophilic cytoplasm and variable mitotic activity. Stromal cells are spindle and densely packed.

Complex hyperplasia without atypia:

Consists of complex ,branched irregular glands with back to back arrangement and scant stroma. Stratification of cells in glands varies from 2 to 4 layers,usually with variable mitotic activity. Stromal cells are spindle and are usually compressed by endometrial glands.

Nuclear features :

Nuclear features in both types , are usually basally oriented oval bland similar to proliferative glands.

Associated with estrogenic stimulation.

ATYPICAL HYPERPLASIA:

Composed of complex patterns of proliferating glands and nuclear atypia.

The nuclei are stratified, shows loss of polarity and also an elevated nuclear and cytoplasmic ratio. Nucleus is round and have a vesicular appearance.

Architectural features are the same in atypical and non atypical hyperplasia.

About 23 to 48 percent of atypical hyperplasia on endometrial sampling present with carcinoma when hysterectomy is done.

The criteria for distinguishing grade 1 endometrioid carcinoma and atypical hyperplasia depends with the identification of stromal invasion by these features

- Desmoplastic stroma with irregular gland infiltration
- Widespread papillary pattern

- Cribriform pattern with confluent glands.

Molecular genetics:

Microsatellite instability, PTEN mutation and KRAS mutation are identified.

***Relationship with carcinoma*:**

Progression to adenocarcinoma is approximately two percent in nonatypical hyperplasia. According to a study incidence of carcinoma following simple hyperplasia is less than 0.4 percent[62].

Conversely incidence of carcinoma with atypical hyperplasia is about 15 to 30 percent [63,64,65,66].About eight percent in simple hyperplasia with atypia and twenty nine percent in complex hyperplasia with atypia.

It was noted that most atypical hyperplasia regressed spontaneously when compared to atypical hyperplasia[66].

According to Mittal et al occurrence of endometrial cancer insitu in complex atypical hyperplasia has elevated incidence of endometrial adenocarcinoma in hysterectomy[67].

Management :

In premenopausal women, conservative approach with regular follow up if the women have nonatypical hyperplasia .In women with atypical hyperplasia progestin suppression can be done.

In perimenopausal women, progestin treatment with regular endometrial biopsies or hysterectomy can be done.

In post menopausal women, the risk of carcinoma is huge hysterectomy is preferred if atypical hyperplasia is diagnosed. If the patient has surgical threat then continuous progestin therapy can be advocated.

ENDOMETRIAL INTRAEPITHELIAL CARCINOMA:

It is the forerunner for serous cancer.It is also known as carcinoma in situ. Not associated with estrogenic stimulation, occurring in the background of endometrial atrophy.

Morphologically consists of cells with atypical nuclei lining the surface and endometrial glands in an atrophic endometrium.

Molecular genetics:

Associated with P53 mutation. Also there is loss of heterozygosity at chromosome 17p.

Management :

Patients are managed by hysterectomy.

ENDOMETRIAL ADENOCARCINOMA:

It is the malignant tumor showing glandular differentiation ,with infiltration in to myometrium.

More than 80 percent of endometrial tumor belong to Type I.

Age group affected are Postmenopausal women ,age range from 2nd to 8th decade. Incidence in women younger than forty years is only 1-8 %[68].

CLINICAL FEATURES:

More than eighty percent of endometrial tumor belong to Type I. Most women affected are postmenopausal but the age range is from second to eighth decade. Incidence of endometrial adenocarcinoma in women younger than 40 years is only 1 to 8 %[69,70]. The tumor is of low grade with minimal invasiveness in young women.

Most but not all of the patients had menstrual irregularity, obesity, infertility and hirsutism.

Most common manifestation is abnormal vaginal bleeding,in some cases it can be asymptomatic[71].

Role of imaging in endometrial carcinoma:

The common investigation in use is the transvaginal ultrasound[72].The endometrial thickness of five millimeter is considered as the upper limit of normal.

Computed tomography or Magnetic resonance imaging can be done for staging for preoperative assessment.

WHO CLASSIFICATION OF ENDOMETRIAL CARCINOMA [ANNEXURE I]:

ENDOMETRIOID ADENOCARCINOMA:

They resemble non neoplastic endometrium in light and electron microscopy.

GROSS:

Presents as a exophytic polypoidal mass or as a diffuse infiltration in to the myometrium. Poorly differentiated tumors are manifested by necrosis.

Endometrial adenocarcinoma usually spreads by direct myometrial invasion,then it disseminates to regional lymph nodes and periuterine structures.

GRADING:

Grading is based on microscopic tumor appearance . According to FIGO and WHO classification Endometrioid adenocarcinomas are divided in to three grades based on amount of solid and glandular areas and nuclear atypia.

Architectural grading is based on the extent of solid areas when compared to well formed glands.

Any type of differentiation in endometrioid carcinoma like squamous type should not be included in grading system.

The architectural appearance can differ from one area to another, the entire tumor architectural appearance should be taken into account for final grading.[TABLE 1&2].

TABLE 1 : Architectural grading of Endometrioid adenocarcinoma

GRADE	DIFFERENTIATION	% OF SOLID AREAS
1	Well differentiated	Less than five percent
2	Mod differentiated	Six to fifty percent
3	Poorly differentiated	More than fifty percent

TABLE 2 : Nuclear grading

GRADE 1	Nuclei oval,mild enlargement,even chromatin.
GRADE 2	Midway between 1 and 3 grades
GRADE 3	Enlarged pleomorphic nucleus,coarse chromatin with prominent nucleoli.

If nuclear grade is higher than the architectural grade then the overall grade is based on nuclear grade.

The frequencies of occurence of grade 1,2,3 Endometrial carcinomas are 50 %,35% and 15% respectively.

Obermair et al stated that Grading of endometrioid carcinoma between curettage and hysterectomy has a fifteen to twenty five percent discordance rate[73].

VARIANTS OF ENDOMETRIOID ADENOCARCINOMA:

- **VILLOGLANDULAR CARCINOMA:**

It ‘s architecture is papillary with fibrovascular core that are delicate lined by columnar cells with bland nuclei[74,75]. This type is better differentiated ,but similar to endometrioid adenocarcinoma.

Common in postmenopausal age group. The nuclear atypia is usually mild to moderate . It has superficial myometrial invasion only.

Modality of management is similar to endometrioid adenocarcinoma.

- **SECRETORY CARCINOMA**:

Resembles secretory endometrium , the uninvolved endometrium shows late secretory pattern. Many cells exhibit prominent supra nuclear or subnuclear vacuoles.

Represents less than two percent of endometrial carcinomas,age group affected are usually postmenopausal women with age ranging from fifty five to fifty eight years[76].

The microscopic picture shows glands which are well differentiated ,lined by unstratified columnar cells with vacuoles in cytoplasm. Grade of the nucleus is usually one.

Treatment modality is similar to endometrioid adenocarcinoma. It carries a favourable prognosis[76].

- **CILIATED CARCINOMA**:

It is a rarely occurring low grade endometrioid carcinoma. Commonly affected age group is post menopausal women. Estrogen therapy has been associated with it.

In microscopy it is similar to endometrioid carcinoma well differentiated type, but the cells have cilia and eosinophilic cytoplasm ,nucleoli is prominent .Ciliated carcinoma has a cribriform pattern.

- **ENDOMETRIOID CARCINOMA - SQUAMOUS DIFFERENTIATION:**

The amount of squamous elements should constitute atleast ten percent in order to consider it as adenocarcinoma containing squamous differentiation.

Depending on the cytology of squamous elements , these can be categorized in to two types

- Adenoacanthoma
- Adenosquamous

But generally these are graded according to the architecture of glandular structures similar to endometrioid adenocarcinoma.

Microscopically, in adenoacanthoma benign squamous structures with keratin pearls and intercellular bridging is seen.

In adenosquamous carcinoma, squamous structures are high grade with atypical nuclei. Behavior depends on the grade, with high grade tumors demonstrating higher rate of invasion and metastasis.

Other types of endometrial carcinoma are,

- **MUCINOUS CARCINOMA**:

It resembles endocervical mucinous carcinoma. To be considered as mucinous type the tumor should demonstrate PAS positivity with resistance to diastase in atleast fifty percent of tumor cells. They usually exhibit a villoglandular architecture lined by columnar cells showing mild stratification.

If the mucin component is less than fifty percent then the tumor can be called like endometrioid carcinoma with mucinous differentiation.

Most of them are of low grade exhibiting good prognosis.

- **SEROUS CARCINOMA**:

Aggressive tumor, about 90 percent cases associated with EIC. It displays a papillary pattern with high nuclear grade.

Patients are usually in postmenopausal age group.

Gross:

It has a papillary and exophytic appearance.The affected uteri are generally small and atrophic.

Microscopy:

Cells have high nuclear to cytoplasmic ratio , high mitotic rate, necrosis, psammoma bodies, complex papillary architecture which are short and fibrotic, some exhibit nuclear hobnailing. It can form tubuloglandular pattern mimicking endometrioid carcinoma[77].

Behavior:

It has a tendency for lymphatic and deep myometrial invasion. So careful staging is mandatory because it has a tendency for extrauterine spread even with minimal invasion of myometrium.

- **CLEAR CELL CARCINOMA:**

It is a TYPE 2 carcinoma. It has a mullerian origin[78]. Common affected women are in the age group of sixty years.

Microscopically, it's a high grade tumor containing pleomorphic cells with nuclear hobnailing and abundant clear cytoplasm in papillary ,tubular and solid patterns.

It’s a high grade tumor presenting in higher stage. Treatment depends on the stage but chemotherapy is given irrespective of tumor stage.

- **MALIGNANT MIXED MULLERIAN TUMOR**:

It also has been included under TYPE 2 carcinoma.

Occurrence is five percent of malignancies in uterine corpus[79].

Occurs commonly in post menopausal women.

Risk factors are

- Obesity
- Nulliparity
- Estrogen intake
- Tamoxifen treatment
- Irradiation of pelvis
- P53 mutation
- PTEN mutation
- Abnormal DNA mismatch repair genes.

Clinically the age group of affected women are usually in their seventies but it has a wider age ranging from 4^{th} to 10^{th} decade of life.

Gross:

It commonly presents as a polypoidal mass protruding through the external os with vaginal bleeding.The tumor is often necrotic.

Microscopy:

Has a biphasic appearance containing both carcinomatous and mesenchymal elements. The epithelial component can be serous/ endometrioid / clear cell/ squamous or mucinous type.

The stromal component can be either homogenous containing spindle cells or it can be heterogenous with chondrosarcomatous or rhabdomyosarcomatous features.

Histopathogenesis:

It is a carcinoma with mesenchymal differentiation ,occurring as a result of metaplasia[80].

Very aggressive variant.

- **UNDIFFERENTIATED CARCINOMA:**

Gross:

Presents as a necrotic polpoidal mass with frequent involvement of lower segment of uterus.

Microscopy:

It exhibits no differentiation. Composed of sheets of discohesive monotonous cells of small to intermediate morphology and prominent nucleoli with no obivious architecture.

It has an abnormality in DNA mismatch repair genes. It has been grouped under TYPE 2 pathogenesis. Has a worst prognosis than a grade 3 endometrioid carcinoma[81]

- **SMALL CELL NEUROENDOCRINE CARCINOMA:**

Its an aggressive tumor .Positive for NSE, cytokeratin and synaptophysin.

- **SQUAMOUS CELL CARCINOMA:**

Pure squamous carcinoma is rare endometrium. Extension from cervical carcinoma should always be ruled out.

For diagnosing squamous cell carcinoma the following criteria is followed

- There should be no connection between the squamous epithelium of endometrium and cervical squamous epithelium
- Adenocarcinoma absent in endometrium
- Cervix does not contain squamous cell carcinoma.

- **UROTHELIAL CARCINOMA:**

Resembles urothelial carcinoma of urinary tract , but has a mullerian profile.

- **HEPATOID CARCINOMA:**

Can be associated with increased AFP.

- **SIGNET RING CELL ADENOCARCINOMA:**

Possibilities of metastasis should always be ruled out.

IMMUNOHISTOCHEMICAL FEATURES:

Endometrioid carcinoma are positive for keratin 7,8,18,19. Most are positive for cytokeratin 7 and negative for cytokeratin 20[82].

Over 80% of cases are positive for vimentin. Coexpression of keratin and vimentin is common [83].

Estrogen and progesterone receptor positivity in FIGO grade 1,2 is higher whereas in grade3 it is seen only in half of the cases[84].

In a study by Rolitsky et al Her2 neu overexpression is seen in 20 percent cases of endometrial adenocarcinoma[85].

Beta catenin and E-cadherin expression is seen in endometrioid carcinoma and absent in serous carcinoma[86].

IMP3 oncofetal protein is expressed in serous carcinoma not in endometrioid carcinoma[87,88].CD117 is expressed in normal endometrium ,also in fifty percent of endometrioid adenocarcinoma[88].

Overexpression of P53 is present in FIGO grade 3 adenocarcinoma .It's positive serous, clear cell and undifferentiated carcinomas[89,90].

THYROID TRANSCRIPTION FACTOR(TTF 1):

TTF 1 marker which is associated with thyroid and lung cancer is also expressed in endometrial adenocarcinoma[91,92].

Zhang PJ et al stated that TTF 1 can also be positive in extrapulmonary adenocarcinoma[93]. In endometrioid carcinoma ,grade 3 adenocarcinomas showed diffuse positivity for TTF 1.Deavers et al studied that there was no correlation between TTF 1 positivity and tumor differentiation[94].

In a study by Zhang et al TTF 1 positivity is about 80% in MMMT [93].

Thyroid transcription factor expression has also been noted in nonneoplastic endometrium,fallopian tube ,endocervix[7].

TTF 1 expression low grade endometrial carcinomas has a poor outcome[6].

Ervine et al[6] showed that TTF 1 expression ; TABLE 3

Low grade endometrial carcinoma	Two percent of cases
Grade 3 carcinoma	Eleven percent of cases
Clear cell carcinoma	Seven percent of cases cases
Serous carcinoma	Nine percent of cases

Napsin A and TTF 1 are used for separation of primary lung carcinoma from metastatic carcinoma like endometrial carcinoma[95].

In a study by jaudah et al ,most endometrial carcinomas are TTF 1 negative. The positive cases expressed only weak positivity and diffuse positivity is not seen in them[7].

For an unknown primary with focal TTF 1 positivity,differential diagnosis of endometrial adenocarcinoma should be considered.

TNM/FIGO (2009) staging (ANNEXURE II):

Changes made in new FIGO(2009) contribution from ISOGP are

- ✓ Carcinomas without invasion in to myometrium and tumors with less than 50 percent invasion of myometrium in STAGE IA.
- ✓ Gland invasion in cervix is eliminated in STAGE II
- ✓ Positive cytology in peritoneal fluid excluded from STAGE IIIA
- ✓ Pelvic , paraaortic nodes metastasis is separated in stage IIIC.

For complete staging Total abdominal hysterectomy with bilateral salpingo – oophrectomy along with pelvic and paraaortic node assessment is needed[96].

When myometrial invasion is 50% or poorly differentiated endometrioid carcinoma with myometrial invasion, adjuvant radiotherapy is given in addition to surgery.

TUMOR SPREAD AND METASTASIS:

Most important route of spread is by lymphovascular invasion. Pelvic,paraaortic nodes and ovaries are the most common sites of extrauterine spread of endometrial adenocarcinoma.

Lymph node metastasis occurs in five to twenty five percent of stage I carcinomas and it is most likely present in high grade invasive tumors[97].

Vaginal vault and pelvis are the most sites for tumor recurrence.

Distant metastasis occurs in lungs, CNS, skin ,liver and bone.

TREATMENT:

Hysterectomy with bilateral salpingo-oophrectomy is the standard treatment modality. Chemotherapy and radiotherapy can be given either preoperatively or postoperatively.

Usually patients are administered postoperative radiotherapy ,if they have poor prognostic conditions.

Patients can be categorized into two groups

- Low risk group - tumors of grade one/two limited to endometrium / has minimal myometrial invasion. Does not require postoperative radiotherapy.
- Intermediate risk group – patients included are those that do not qualify into low/ high risk groups.
- High risk group - patients with adnexal involvement, nodal metastasis .Thes patiemts require postoperative radiotherapy.

Recurrent tumors are treated with hormone, radiation and cytotoxic therapy.

PROGNOSTIC FACTORS:

- **AGE:**

Young women mostly have low grade tumors. One study suggests decreased life span for women more than 50 years of age[98].

- **GRADE:**

Prognosis for high grade tumors is poor regardless of their histologic type[99]. Women having low grade endometrial carcinoma limited to inner half of myometrium have a five year survival rate of hundred percent, where as patients with low grade tumor morphology but presenting at a higher stage have a five year survival rate of sixty seven percent. similarly high grade tumors at advanced stages have only twenty six percent five year survival rate[100].

- **MYOMETRAL INVASION:**

It is an important factor in prognosis.The depth of invasion is related to number of nodal metastasis, incidence of pelvic node metastasis rises to twenty five percent in tumors showing greater than fifty percent myometrial invasion.

- **INVOLVEMENT OF CERVIX:**

Tumors without extrauterine involvement but with cervical invasion is associated with an increased risk of recurrence rate of about sixteen percent [101].

- **STAGE :**

It helps to plan the treatment method. Myometrial invasion greater than 50 percent is associated with worst prognosis[102].

- **TUMOR TYPE:**

Clear cell carcinoma, Papillary serous carcinoma, MMMT tumors are highly aggressive than the high grade variants of endometrioid carcinoma[103,104].

- **LYMPHOVASCULAR INVASION:**

It's a poor prognostic factor [105].

- **PERITONEAL WASH:**

Positivity of tumor cells in the peritoneal fluid is an independent determinant of increased recurrence and decreased survival[106].

- **PLOIDY:**

Aneuploid tumors are high grade tumors and has worst prognosis[107].

- **ANGIOGENESIS:**

Increased vascularity is associated with decreased survival[108].

MATERIALS AND METHODS

MATERIALS AND METHODS

This study is a prospective and retrospective study of endometrial cancer in hysterectomy specimens conducted in the Institute of pathology at Institute of obstetrics and gynaecology ,Madras Medical College and Rajiv Gandhi Government General Hospital,Chennai during the period between January 2010 to December 2014.

A total of 17,032 cases were submitted to our Institute of pathology, at Institute of obstetrics and gynaecology Madras medical college during the period of January 2010 to December 2014 for histopathological examination. Out of them 93 cases of endometrial carcinoma in hysterectomy specimens were reported.

Inclusion criteria:

Patients diagnosed as Endometrial adenocarcinoma - conventional type & its variants, Malignant mixed mullerian tumor of uterus.

Exclusion criteria:

Benign tumors and non epithelial tumors of uterus. Cases for which only fractional curettage was done.

METHOD OF DATA COLLECTION:

Detailed history of the cases regarding age, menstrual status, clinical history, parity, fractional curettage and staging laparatomy were obtained for all the 93 endometrial carcinoma cases reported during the period of study from surgical pathology records. Hematoxylin and Eosin stained 4 µ thick sections of the paraffin tissue blocks of specimens were reviewed. The following clinical and pathological parameters were evaluated: Age, parity, menstrual status, tumour type, tumour grade, stage.

Endometrioid carcinoma was classified as well differentiated, moderately differentiated, poorly differentiated based on differentiation. Among 93 cases endometrial carcinoma 53 cases were well differentiated endometrioid adenocarcinoma including one villoglandular variant,15 cases were moderately differentiated endometrioid carcinoma , 16 cases were poorly differentiated endometrioid carcinoma , 1 case of serous carcinoma, 3 cases clear cell carcinoma , 4 cases malignant mixed mullerian tumour and 1 case of undifferentiated carcinoma.

Among 93 cases, 50 cases were randomly selected and their representative formalin fixed and paraffin embedded tissue samples was subjected for TTF 1 immunohistochemistry.

IMMUNOHISTOCHEMICAL EVALUATION:

Immuohistochemical analysis of marker TTF 1 was done in paraffin embedded tissue samples using Super-sensitive polymer HRP system based on non-biotin polymeric technology.[TABLE 4]. 4 µ thick sections from formalin fixed and paraffin embedded tissue samples was transferred onto gelatin coated slides. Heat induced antigen retrieval was done. The antigen was bound with rabbit monoclonal antibody (Pathnsitu) against TTF 1 protein and then detected by adding secondary antibody conjugated horse radish peroxidase-polymer and diaminobenzidine substrate. Step by step procedure of Immunohistochemistry is given in **Annexure III**.

TABLE 4: TTF 1 MARKER

Antigen	**Vendor**	**Species(clone)**	**Dilution**	**Positive control**
TTF 1	PATHNSITU	Rabbit	Ready to use	Thyroid

INTERPRETATION AND SCORING SYSTEM:

The immunohistochemically stained slides were analyzed for the presence of reaction, nuclear localization, percentage of cells stained and intensity of reaction.

SCORING OF TTF 1:

TTF 1 nuclear staining was scored based on scoring done by W Glen McCluggage[6].

1) Negative (absent)
2) Focal (< 50 % nuclear staining)
3) Diffuse (>50% nuclear staining)

STATISTICAL ANALYSIS:

- Immunohistochemical analysis was done in paraffin embedded tissue samples using the statistical package for social science software version IBM SPSS version 20 which consisted computing the frequency counts and percentages for qualitative variables and mean for quantitative variables.
- The correlation between TTF1 expression and various parameters was calculated using pearson chi square test.
- P value 0.05 was considered as a cut-off point for determination of statistically significant results.

OBSERVATION

AND

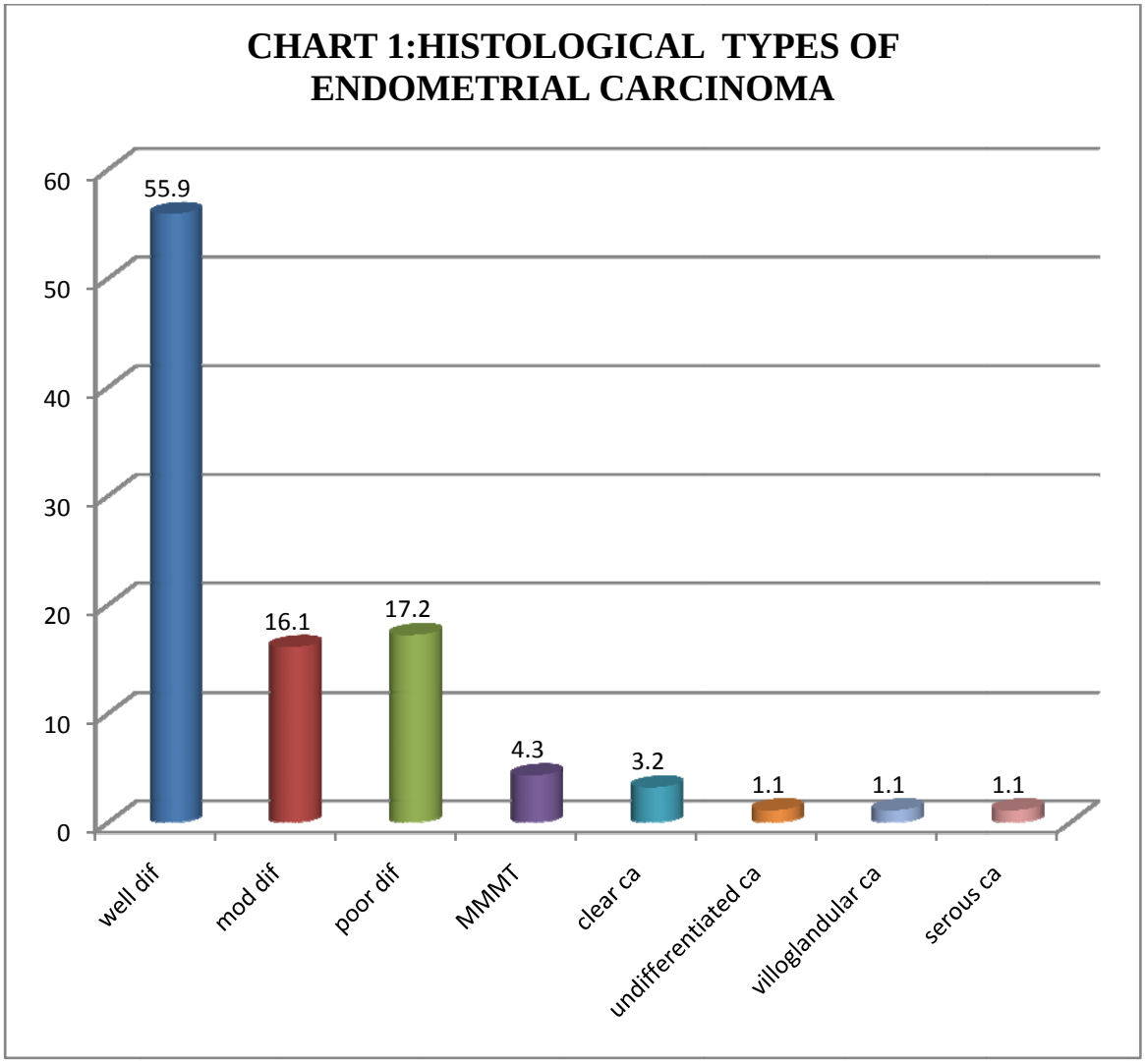
RESULTS

OBSERVATION AND RESULTS

In the study period of 5 years from January 2010 to December 2014,a total of 17032 specimens were received in the Institute of obstetrics and gynaecology, Madras Medical College for histopathological examination. Total number of endometrial carcinoma in hysterectomy specimens were 93 cases during this five year period.

TABLE 5 : HISTOLOGICAL TYPES OF ENDOMETRIAL CARCINOMA

Histological types	Number of cases	Percentage
Welldifferentiated endometrioid carcinoma	52	55.9%
Moderately differentiated endometrioid carcinoma	15	16.1%
Poorlydifferentiated endometrioid carcinoma	16	17.2%
MMMT	4	4.3%
Clear cell carcinoma	3	3.2%
Villoglandular carcinoma	1	1.1%
Serous carcinoma	1	1.1%
Undifferentiated ca	1	1.1%



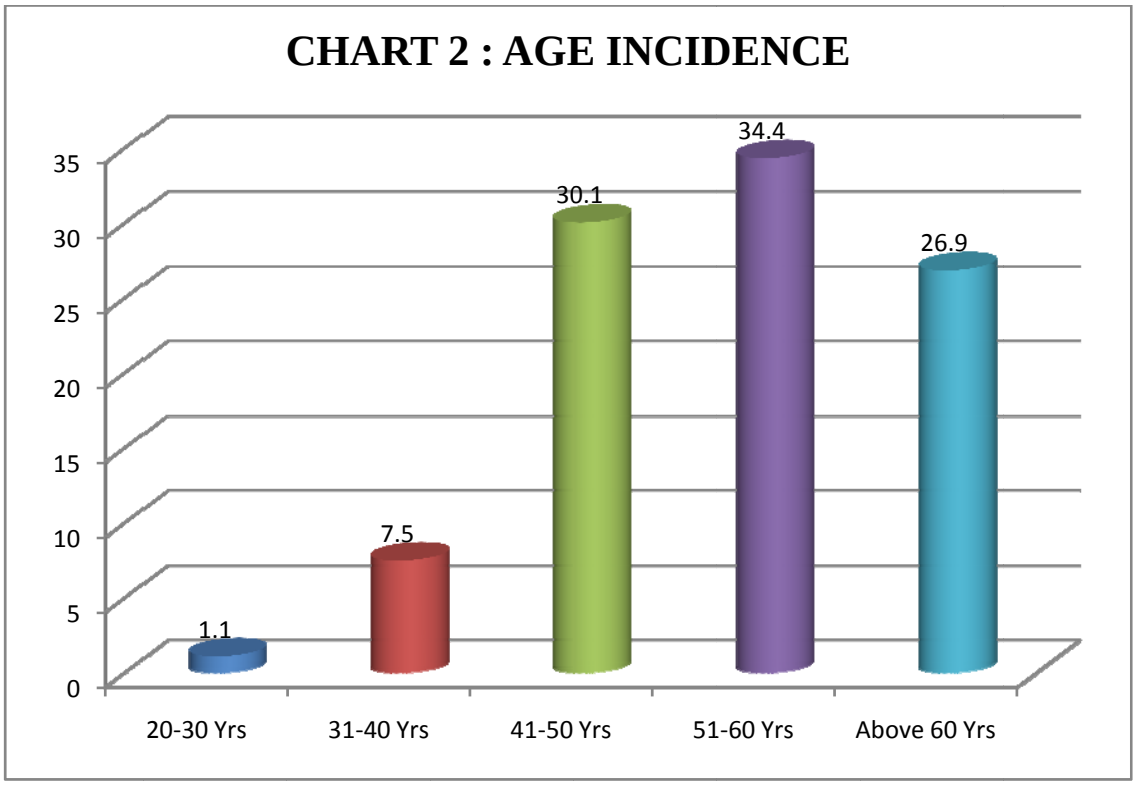
Among 93 cases of endometrial carcinoma 53 cases were well differentiated endometrioid adenocarcinoma including one villoglandular variant,15 cases were endometrioid adenocarcinoma moderately differentiated , 16 cases were endometrioid adenocarcinoma poorly differentiated , 1 serous carcinoma, 3 clear cell carcinoma , 4 cases of malignant mixed mullerian tumour and 1 case of undifferentiated carcinoma were reported.[TABLE5 &CHART 1].

Age group affected:

Peak incidence of endometrial carcinoma is in the age group fifty one to sixty years. [TABLE 6 & CHART 2].

TABLE 6: AGE INCIDENCE

Age group	Number of cases	Percentage
20-30 years	1	1.1%
31-40 years	7	7.5%
41-50 years	28	30.1%
51-60 years	32	34.4%
Above 60 years	25	26.9%



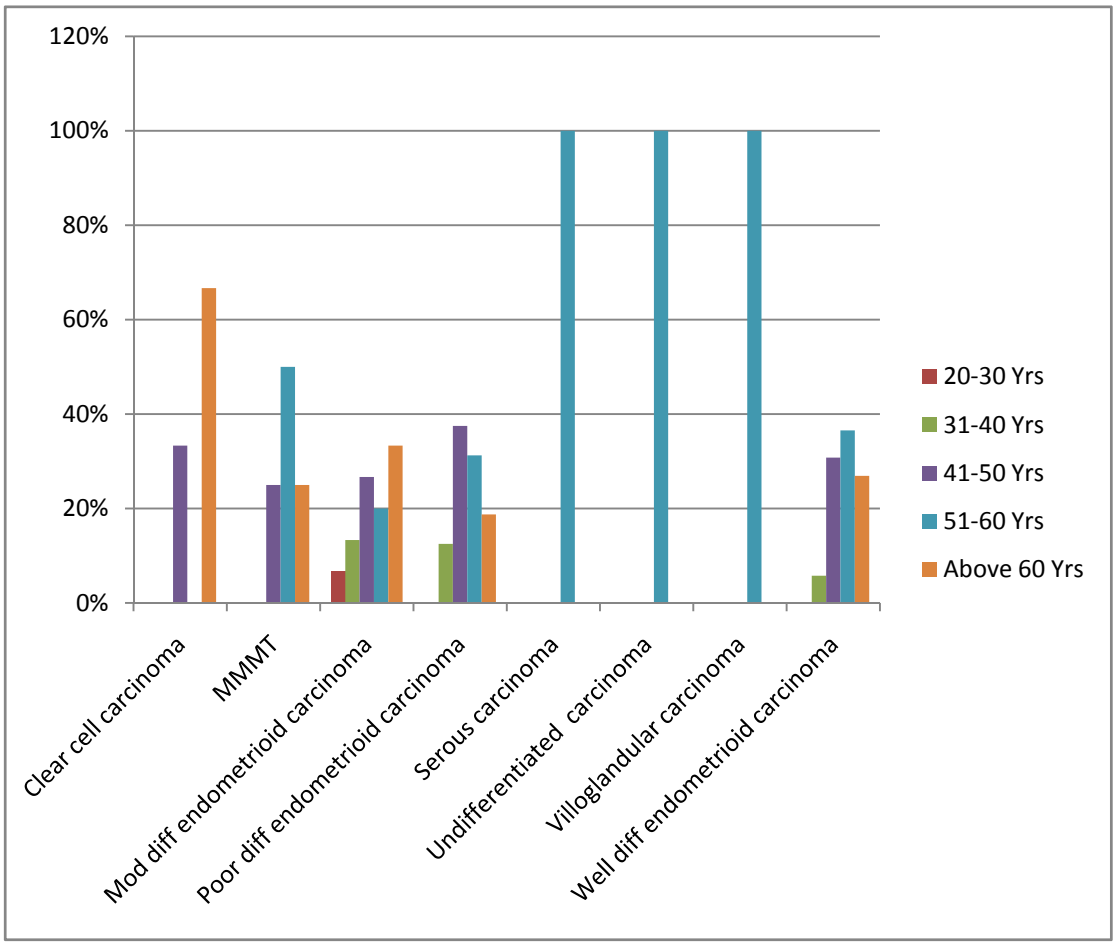
In this study about 32 cases are reported in age group fifty one to sixty years years. The youngest age and oldest age at which endometrial carcinoma was diagnosed in this study is 27 years and 78 years.

Age group and histological types of endometrial carcinoma:

TABLE 7:AGE GROUP AND HISTOLOGICAL TYPE

Age group	Histological type								Total
	Clear ca	MMMT	Mod diff	Poor dif	Serous ca	Undif ca	VG ca	Well dif	
20-30 Yrs	0	0	1	0	0	0	0	0	1
31-40 Yrs	0	0	2	2	0	0	0	3	7
41-50Yrs	1	1	4	6	0	0	0	16	28
51-60Yrs	0	2	3	5	1	1	1	19	32
> 60 Yrs	2	1	5	3	0	0	0	14	25
Total	3	4	15	16	1	1	1	52	93

CHART 3 : AGE GROUP AND HISTOLOGICAL TYPE



On assessing age incidence of different types of endometrial carcinoma, 1 case moderately differentiated endometrial carcinoma has been reported in the age group 20 – 30 years.[TABLE7 & CHART 3].

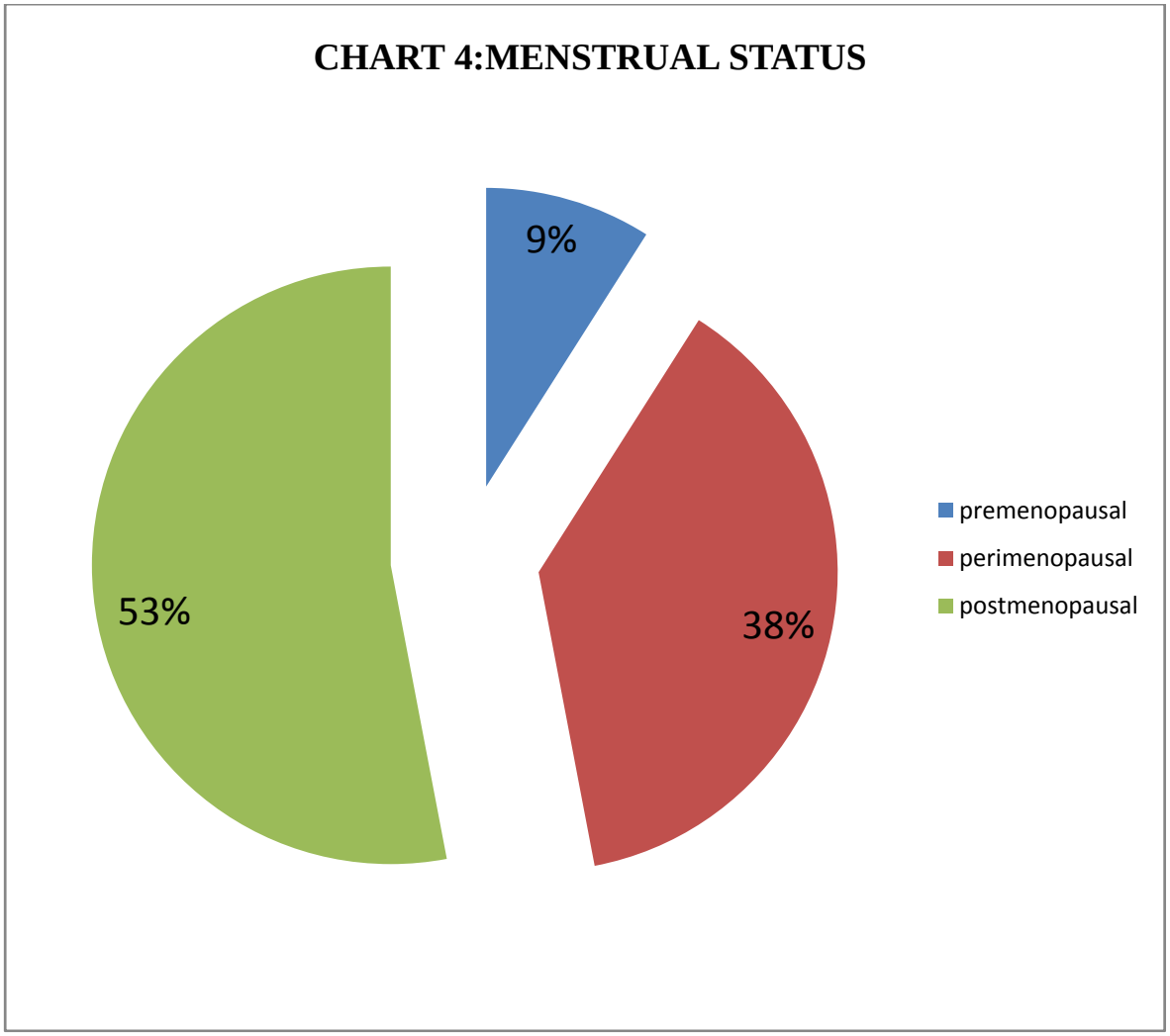
Maximum of 32 cases were diagnosed in the age group 51 – 60 years. Out of them 19 were well differentiated endometrioid carcinoma,5 cases of grade 3 endometrioid carcinoma,3 cases of grade 2 endometrioid carcinoma,2 cases malignant mixed mullerian tumour and 1 case each in serous, undifferentiated and villoglandular carcinomas .

About 2 cases of clear cell carcinoma ,5 cases of moderately differentiated, 3 cases of poorly differentiated and 14 cases of well differentiated endometrioid carcinoma were diagnosed in women above 60 years.

Menstrual status:

TABLE 8 : MENSTRUAL STATUS

Menstrual status	Number of cases	Percentage
Premenopausal	8	8.6%
Perimenopausal	35	37.6%
Postmenopausal	50	53.8%



Women are grouped in to 3 categories , women aged less than 40 years are categorized in the premenopausal age group, women aged within 40 to 55 years and women over 55 years are included in perimenopausal and postmenopausal category.[TABLE 8&CHART 4].

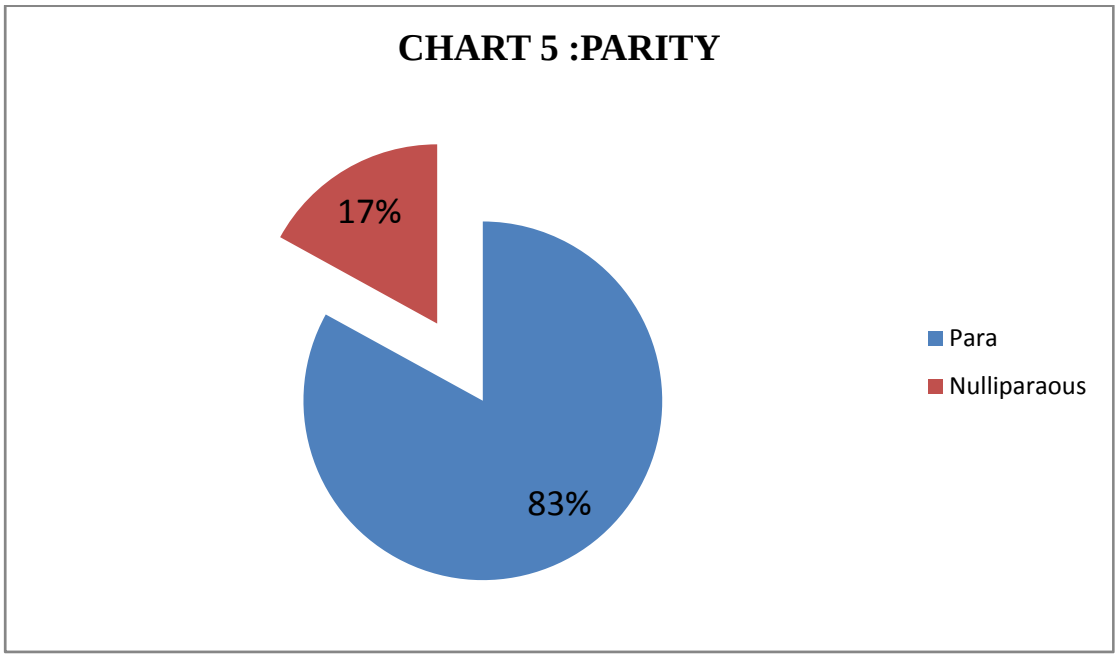
In this study, out of the 93 cases maximum of 50 cases were reported with a percentage of 53.8% in the postmenopausal age group. In perimenopausal women 35 cases and 8 cases in premenopausal women.

Parity :

TABLE 9 : PARITY AND ENDOMETRIAL CARCINOMA

Parity	Number of cases	Percentage
Parous	77	82.8%
Nulliparous	16	17.2%

CHART 5 :PARITY

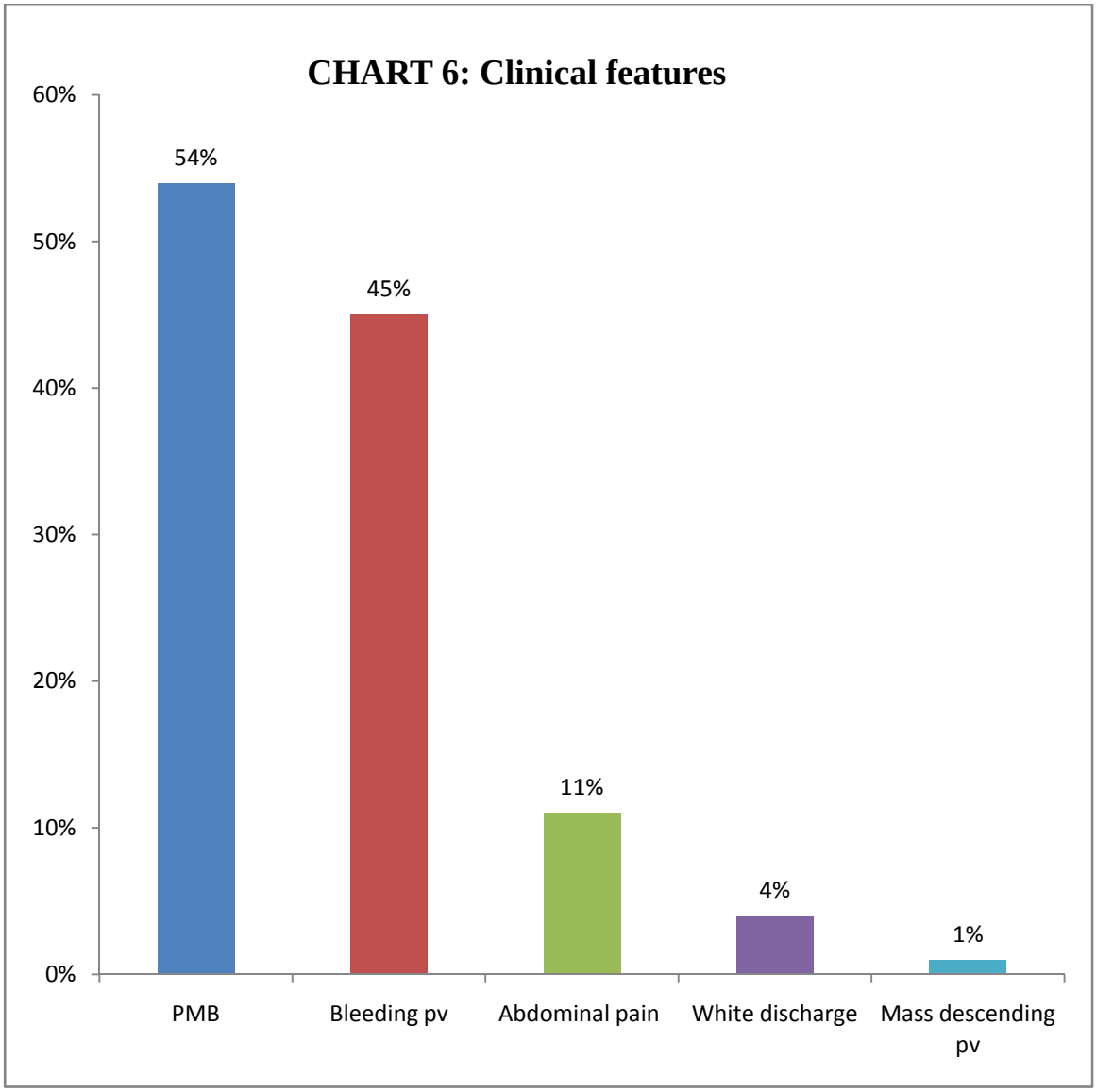


In this study majority of women with endometrial carcinoma are parous having a frequency of 77 cases with a percentage of 82.8 % and 17.2 % women are nulliparous.[TABLE 9&CHART 5].

Clinical features : [TABLE 10 &CHART 6]

TABLE 10 : CLINICAL FEATURES

Symptoms	**Percentage**
Post menopausal bleeding	54%
Bleeding pv	45%
Abdominal pain	11%
White discharge	4%
Mass descending per vagina	1%



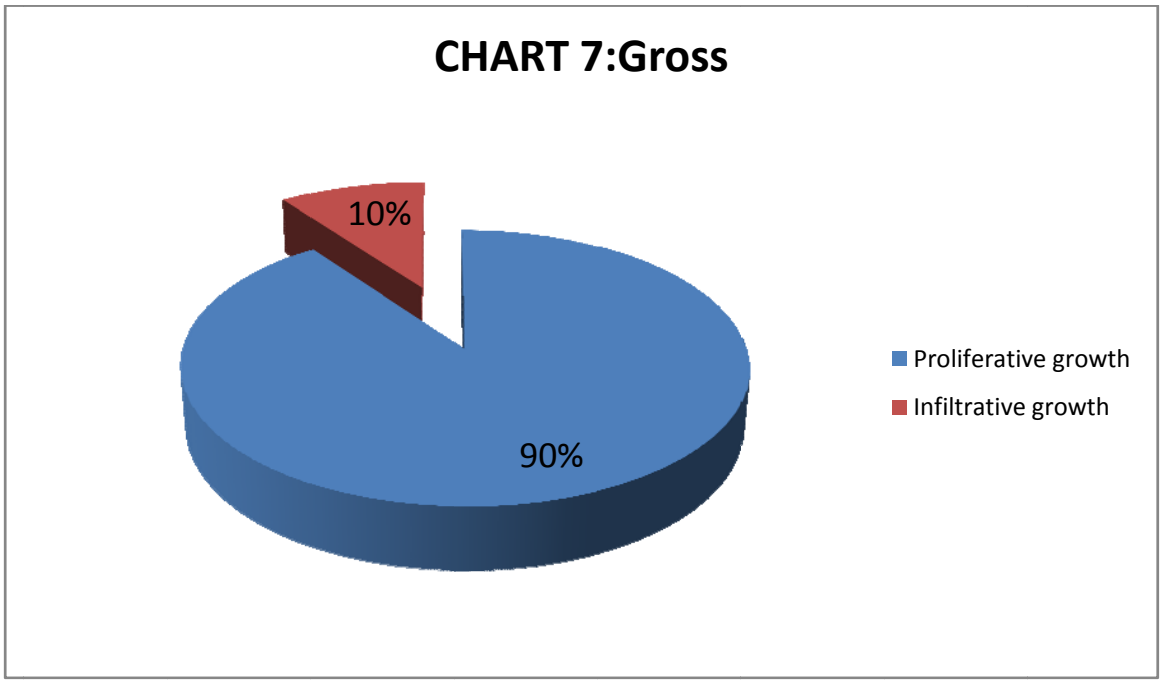
In this study majority of women about 54% presented with postmenopausal bleeding. About 45 % women had irregular bleeding per vagina, 11% presented with abdominal pain, 4 % with white discharge and 1 % with mass descending per vagina.

Gross :

In this study about 50 cases were randomly selected and their gross features were assessed.[TABLE 11&CHART 7].

TABLE 11: GROSS FEATURES

Gross	Number of cases	Percentage
Proliferative growth	45	90%
Infiltrative growth	5	10%



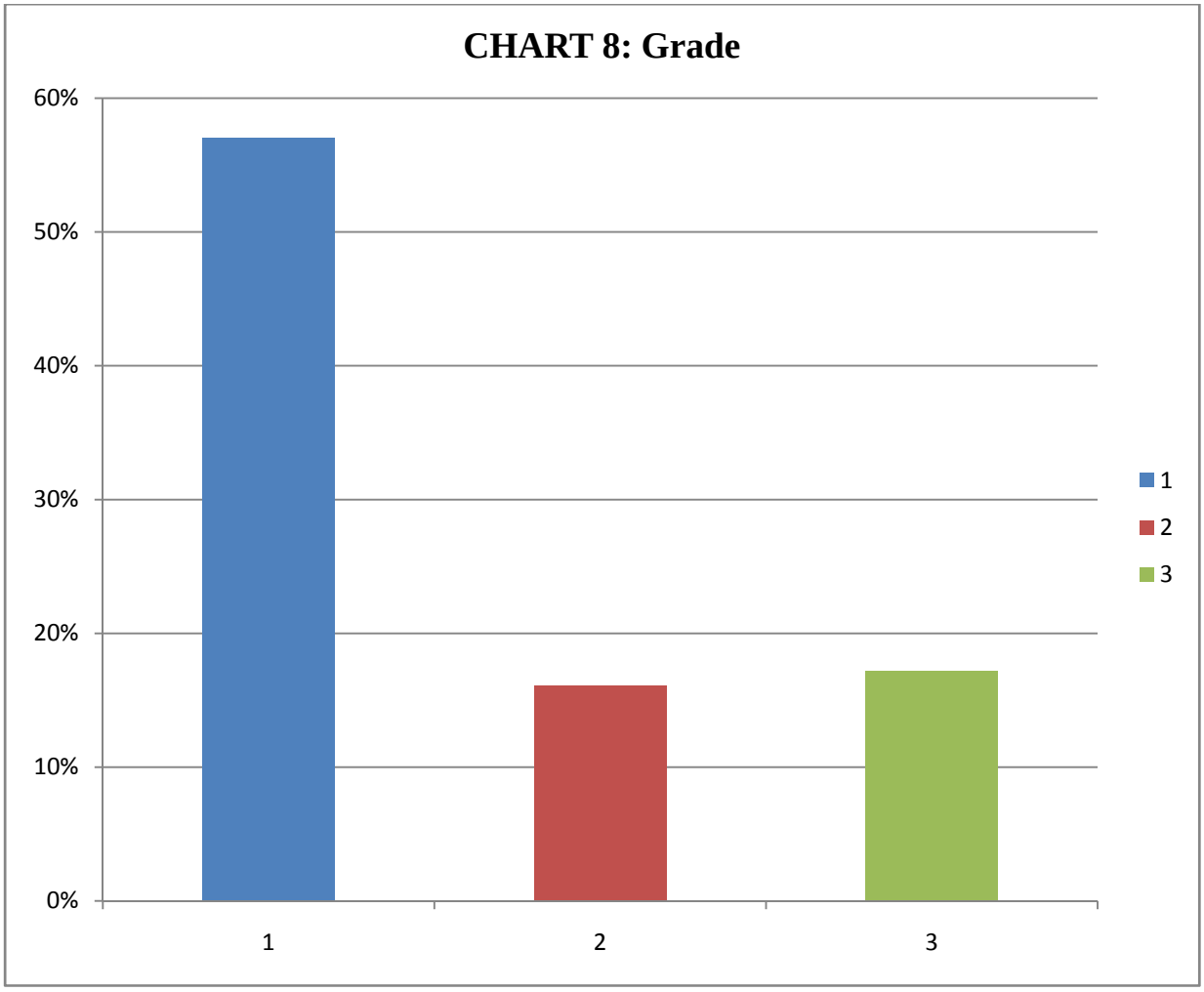
About 90% of endometrial carcinoma in our study presented grossly with proliferative growth.

During this 5 year study, the majority of cases were well differentiated endometrioid carcinoma accounting for 55.9% of total cases.

Grade of endometrioid carcinoma: [TABLE12&CHART 8].

TABLE 12: Different grades of endometrioid carcinoma

Grade	Number of cases	Percentage
1	53	57%
2	15	16.1%
3	16	17.2%

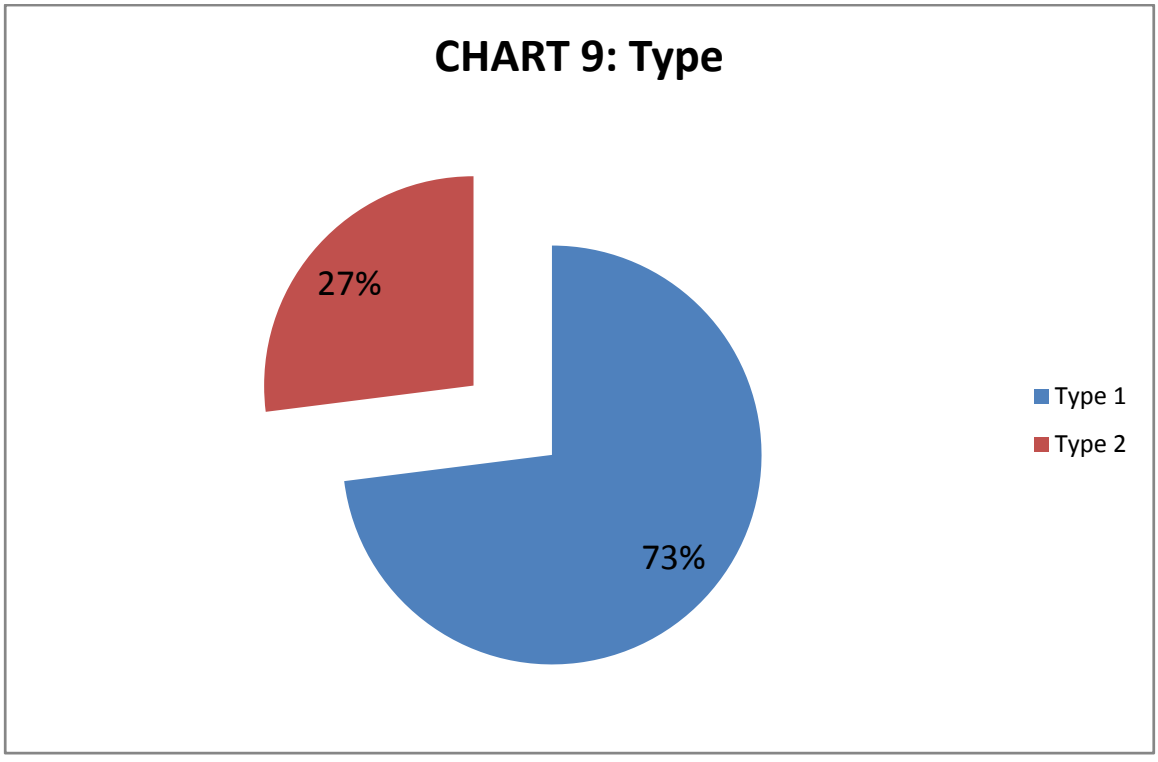


The incidence of different grades of endometrioid carcinoma in the 5 year period from January 2010 to December 2014 were 57 % for grade 1 endometrioid carcinoma including villoglandular carcinoma, 16.1% for grade 2 endometrioid carcinoma and 17.2% for grade 3 endometrioid carcinoma. Among different grades of endometrial carcinoma well differentiated grade has the commonest occurrence in this 5 year study.

Type of endometrial carcinoma:

TABLE 13: Type of endometrial carcinoma

Type	Number of cases	Percentage
1	68	73.1%
2	25	26.9%



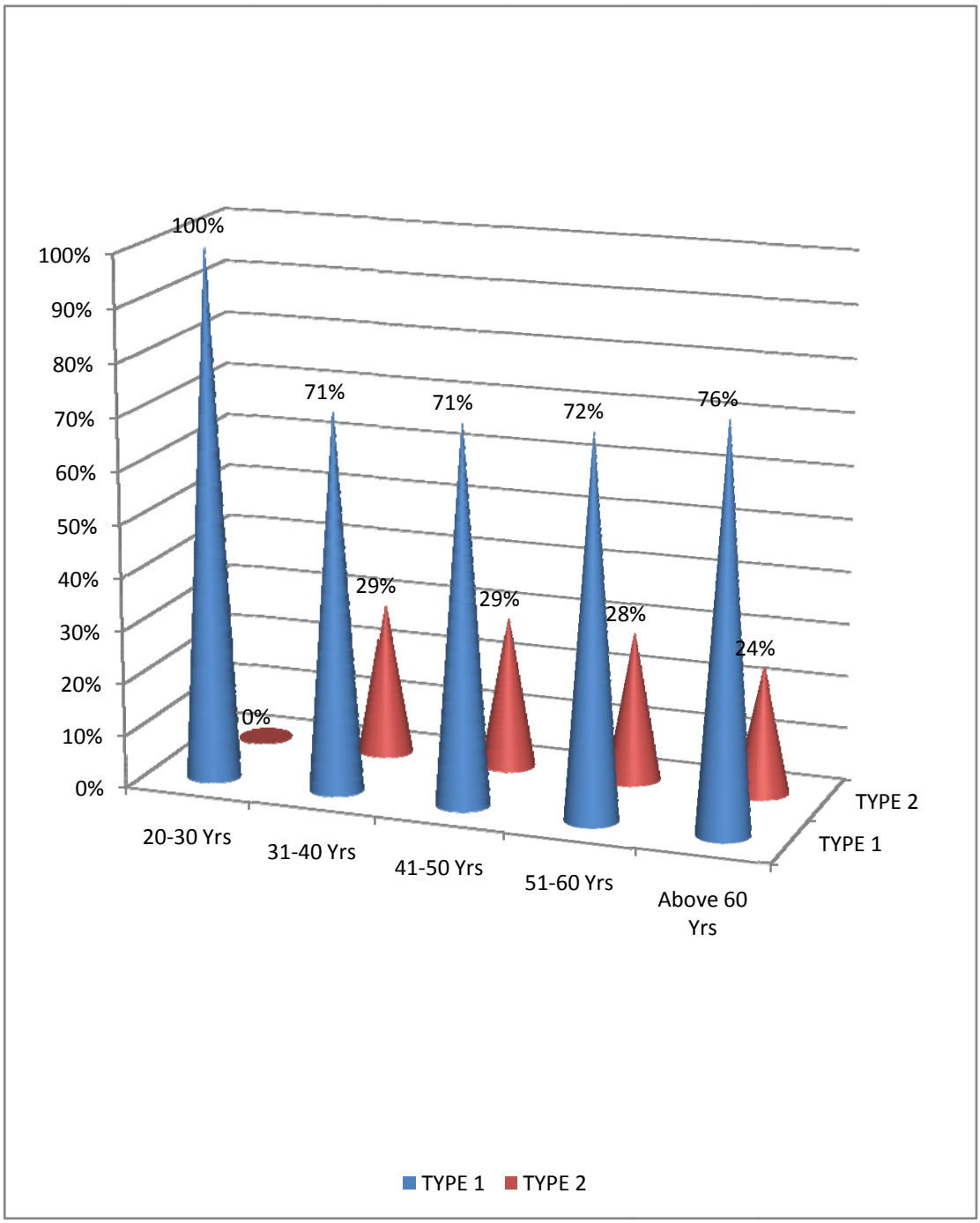
In this study incidence of Type 1 carcinoma is 73% and Type 2 carcinoma is 27%.[TABLE13&CHART 9].

Comparison between TYPE of endometrial carcinoma and Age group :[TABLE 14&CHART10]

TABLE 14 : TYPE and age group

Age group	Type 1	Type 2	Total
20-30 yrs	1	0	1
31-40yrs	5	2	7
41-50yrs	20	8	28
51-60 yrs	23	9	32
Above 60 yrs	19	6	25

CHART 10: Comparison between TYPE and age group



Most of type I and type 2 carcinoma occurred in the age group of 51 to 60 years in this study.

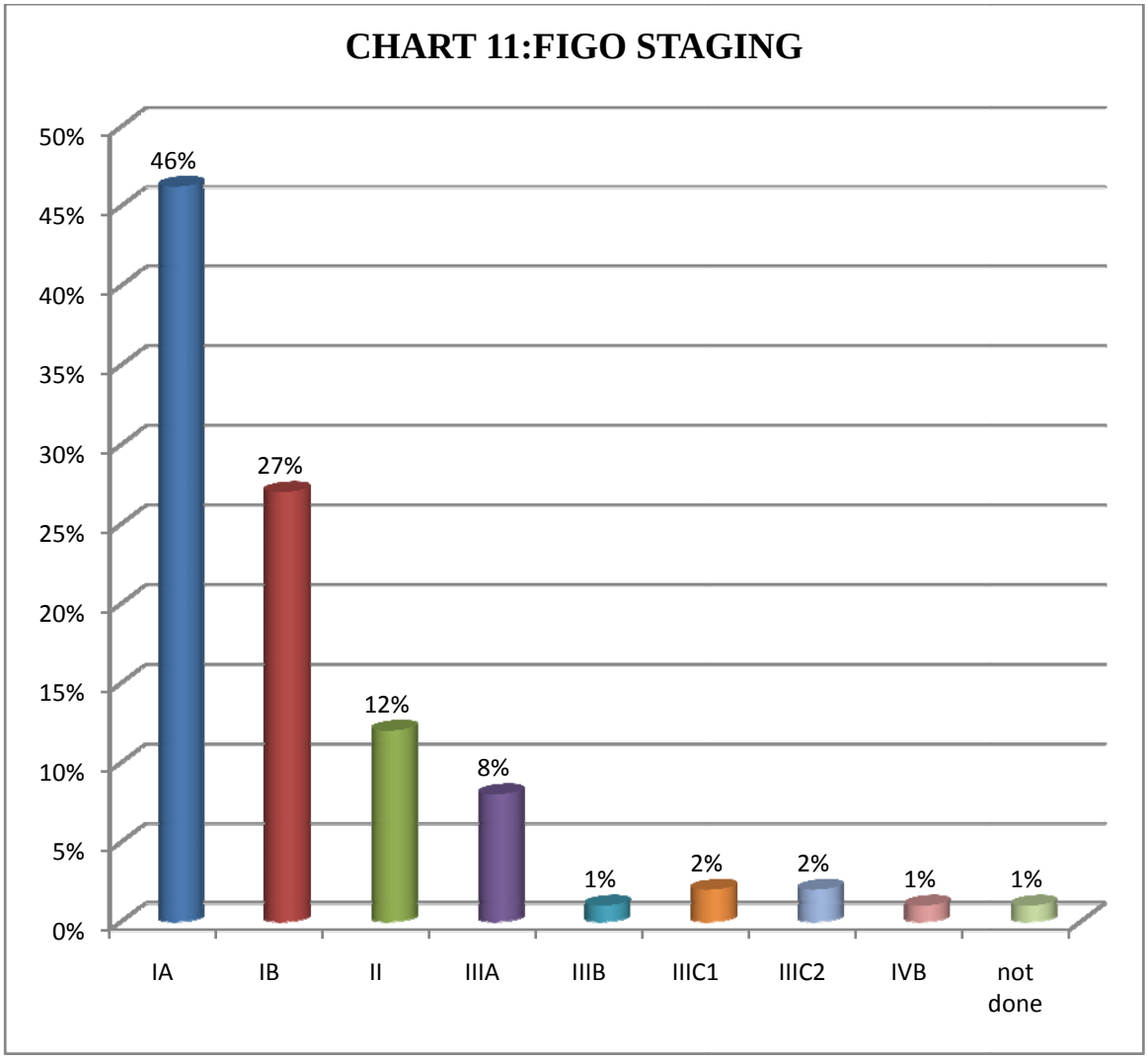
FIGO Stage:

TABLE 15: FIGO STAGING OF ENDOMETRIAL CARCINOMA

Stage	Number of cases	Percentage
IA	43	46.2%
IB	25	26.9%
II	11	11.8%
IIIA	7	7.5%
IIIB	1	1.1%
IIIC1	2	2.2%
IIIC2	2	2.2%
IVA	-	-
IVB	1	1.1%
Not done	1	1.1%

Majority of cases of endometrial carcinoma in this 5 year study presented in stage IA with a percentage of 46.2%, 25 cases presented in stage IB ,11 cases in stage II,7 cases in stage IIIA, 1 case in stage IIIB,2 cases each in stage IIIC1 and IIIC2,1 case in stage in stage IVB.In one case the specimen was received in piecemeal so staging was not done.

[TABLE15&CHART11].



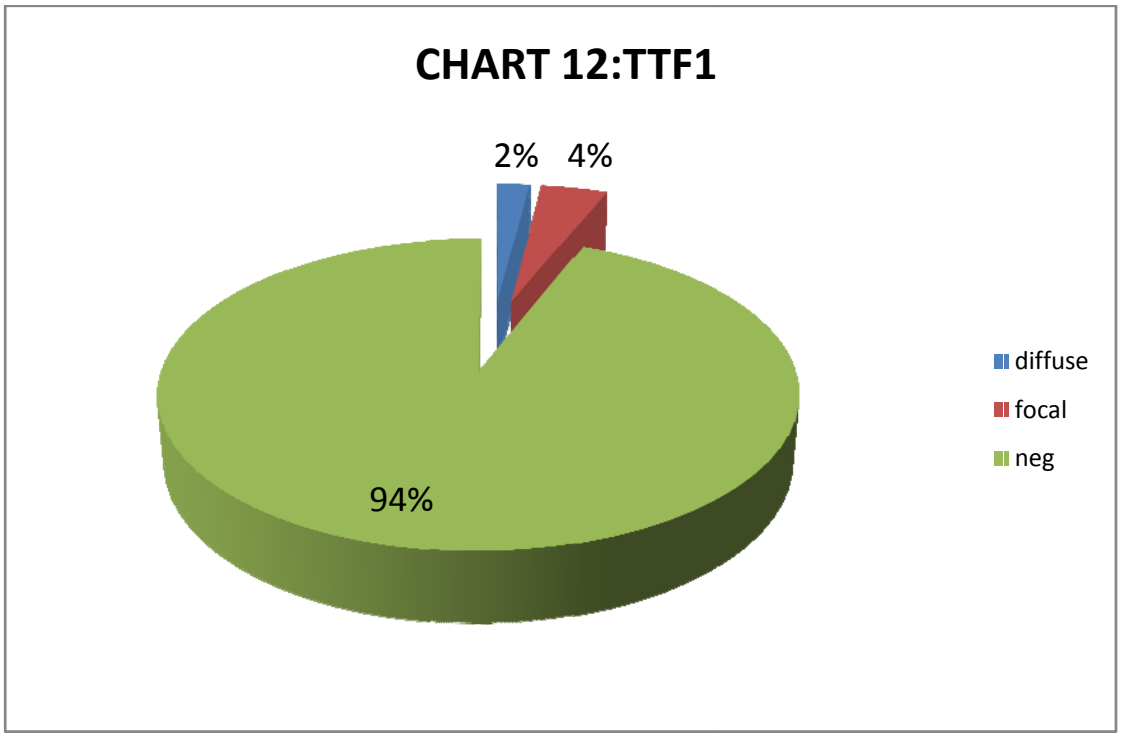
TTF 1 expression in endometrial carcinoma:

In this study randomly for 50 cases of endometrial carcinoma TTF1 immunohistochemistry was done.

It is graded as focal (less than 50% staining),diffuse (more than 50% staining) and negative.[TABLE16&CHART12].

TABLE 16: TTF1 expression in endometrial carcinoma

TTF1 expression	Number of cases	Percentage
Diffuse	1	2%
Focal	2	4%
Negative	47	94%



In our study out of the 50 cases only 3 cases are positive for TTF 1.

TTF 1 expression and grade of endometrial carcinoma:

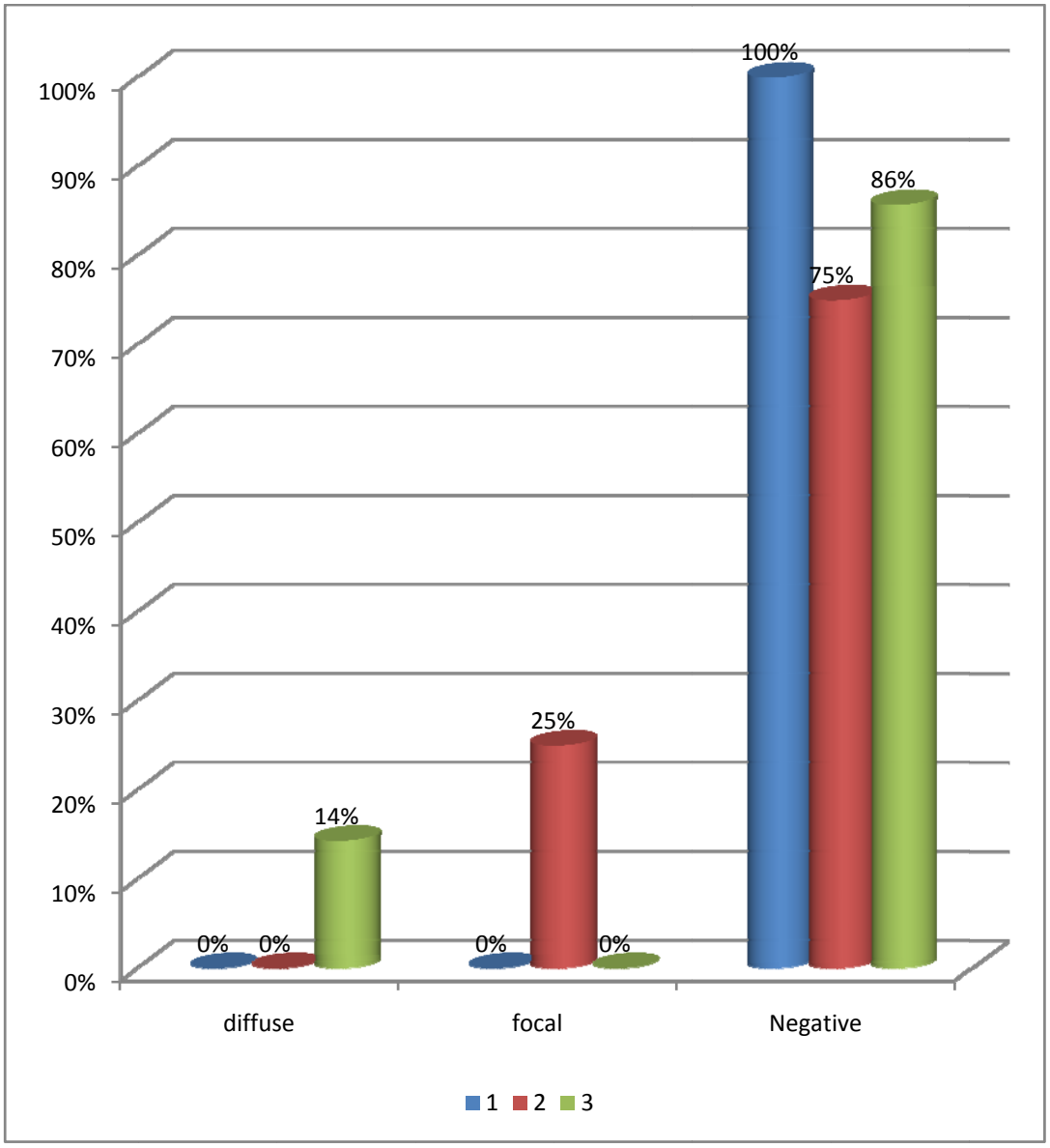
TABLE 17:TTF1 expression with grade

TTF 1 expression			GRADE			Total
			1	2	3	
TTF1	diffuse	Count	0	0	1	1
		%	0.0%	0.0%	14.3%	2.2%
	Focal	Count	0	2	0	2
		%	0.0%	25.0%	0.0%	4.4%
	Neg	Count	30	6	6	42
		%	100.0%	75.0%	85.7%	93.3%
	Total	Count	30	8	7	45
		%	100.0%	100.0%	100.0%	100.0%

p=0.004*

In this study for 30 cases of well differentiated endometrioid carcinoma (Grade 1),8 cases of Grade 2,7 cases of Grade 3 endometrioid carcinoma, 2 clear cell carcinoma and 3 MMMT ,TTF1 marker was done.

CHART 13:TTF1 expression and grade



On correlating TTF1 expression with grade of endometrioid carcinoma diffuse positivity was present for one case of poorly differentiated endometrioid carcinoma, focal positivity was present for 2 cases of moderately differentiated endometrioid carcinoma.[TABLE17&CHART13].

The p value is 0.004, suggesting that its statistically significant.

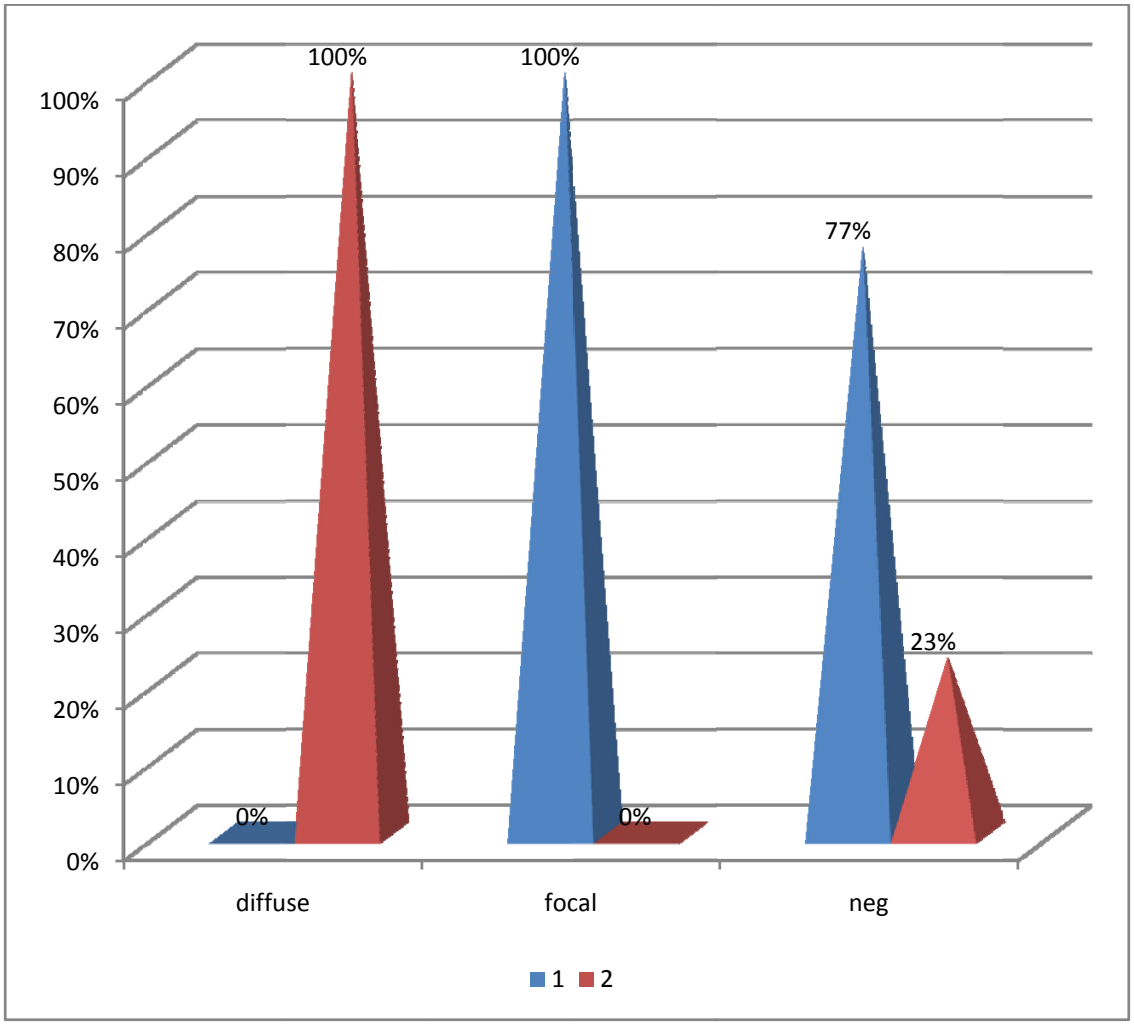
TTF 1 and TYPE of endometrial carcinoma:

TABLE 18: TTF 1 and TYPE of endometrial carcinoma

TTF1	TYPE 1	TYPE 2
Diffuse	0	1
Focal	2	0
Negative	36	11

On studying the expression of TTF 1 in relation to type of endometrial carcinoma, out of 12 cases in type2,a diffuse positivity was noted in one case of type 2 – poorly differentiated endometrioid carcinoma.In type 1 carcinoma out of 38 cases, focal positivity was observed in 2 cases of moderately differentiated endometrioid carcinoma.[TABLE 18&CHART14]

CHART 14 :TTF 1 and TYPE of endometrial carcinoma



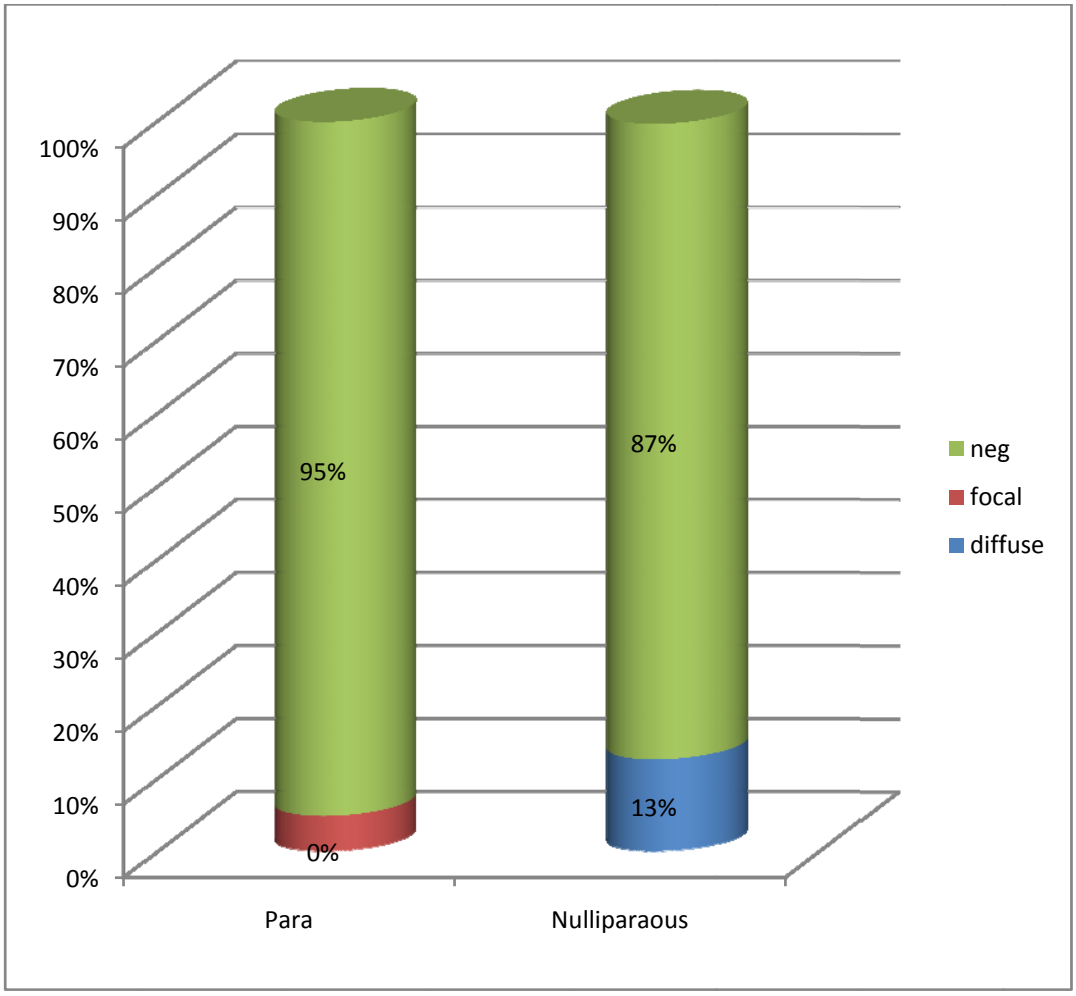
Comparison of TTF 1 positivity with parity:

In the 50 cases for which TTF1 immunostain was done, nullipara women were 8 cases and para women were 42 cases. [TABLE19 & CHART15].

TABLE 19: TTF 1 and parity

TTF 1	Para	Nullipara
Focal	2	0
Diffuse	0	1
Negative	40	7

CHART 15 :TTF 1 and parity

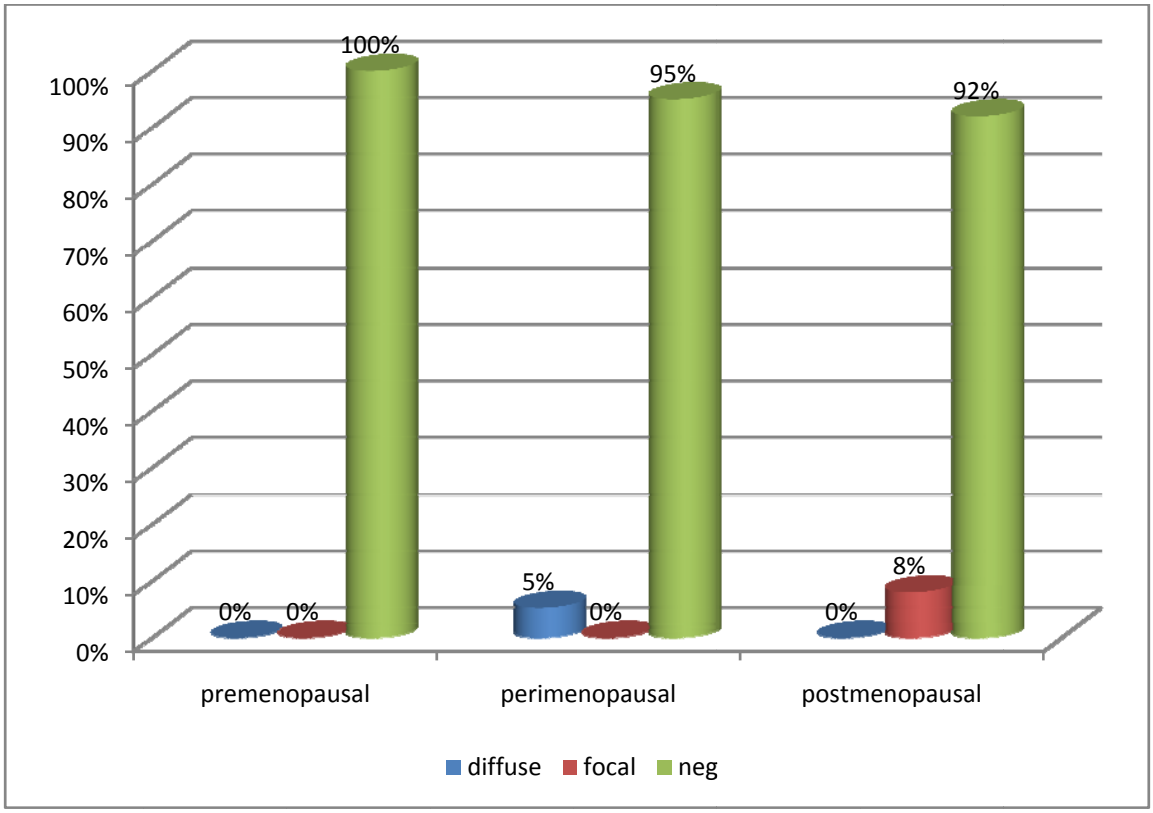


TTF 1 and menstrual status: [TABLE 20&CHART16].

TABLE 20 : TTF 1 and menstrual status

Menstrual status	TTF1			Total
	diffuse	focal	neg	
Premenopausal	0	0	6	6
Perimenopausal	1	0	18	19
Postmenopausal	0	2	23	25
Total	1	2	47	50

CHART 16: TTF 1 and menstrual status



The TTF 1 positive cases fall under the peri menopausal and post menopausal age group.

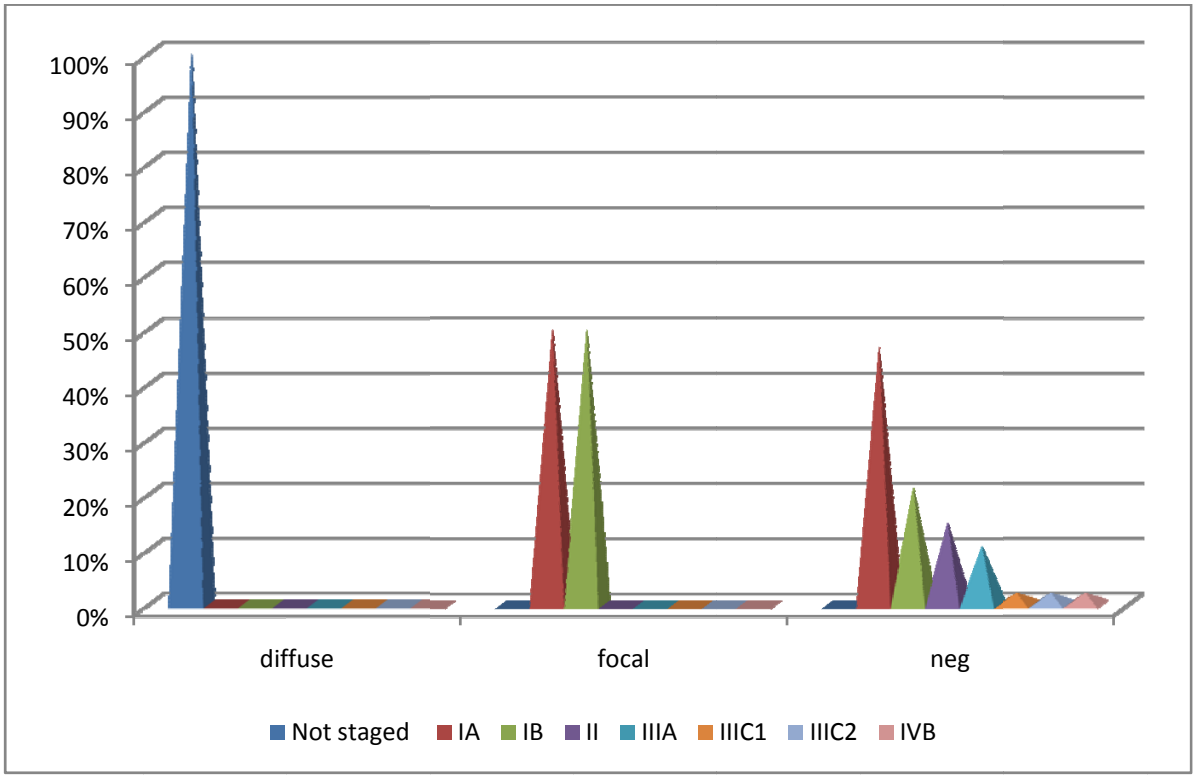
TTF 1 expression with stage of endometrial carcinoma:

TTF 1 and stage of endometrial cancer is studied.

TABLE 21: TTF 1 and stage

TTF 1	FIGO_STAGE									
	Not staged	IA	IB	II	IIIA	IIIC1	IIIC2	IVA	IVB	**Total**
Diffuse	1	0	0	0	0	0	0	0	0	1
Focal	0	1	1	0	0	0	0	0	0	2
Neg	0	22	10	7	5	1	1	0	1	47
Total	1	23	11	7	5	1	1	0	1	50

CHART 17 : TTF 1 and stage



On comparing TTF 1 positivity with FIGO stage , 2 focally positive cases of moderately differentiated endometrioid carcinoma were in stage IA and IB . Diffuse positive case of poorly differentiated endometrioid carcinoma was not staged as it was received in piece meal.[TABLE21&CHART 17].

This association was statistically significant with a p value of <= 0.001.

PICTURES

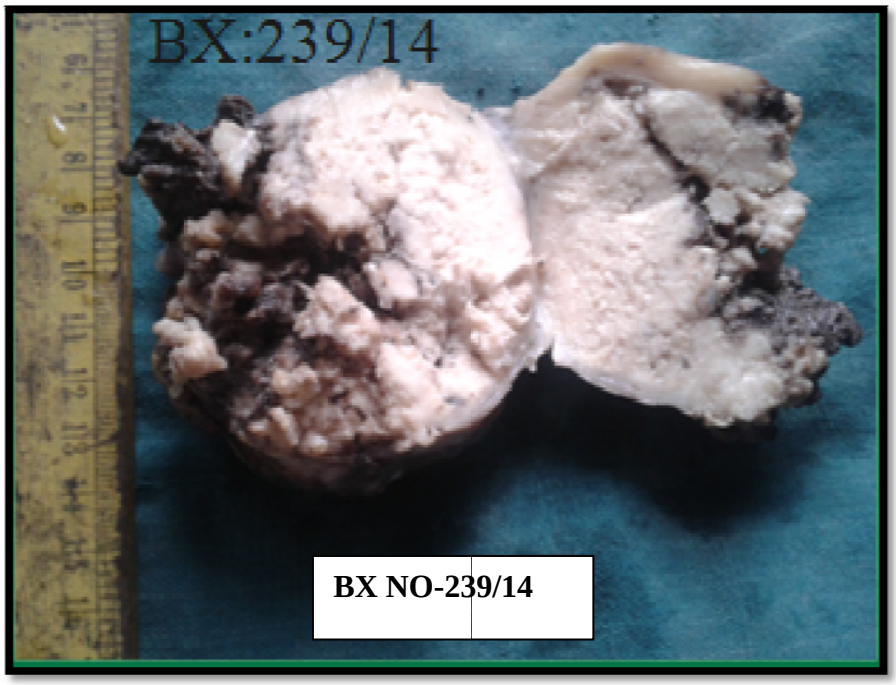


FIGURE :1 – GROSS –Well differentiated endometrioid adenocarcinoma of uterus presenting as a proliferative growth.

FIGURE :2 – GROSS –Moderately differentiated endometrioid adenocarcinoma of uterus presenting as a proliferative growth.

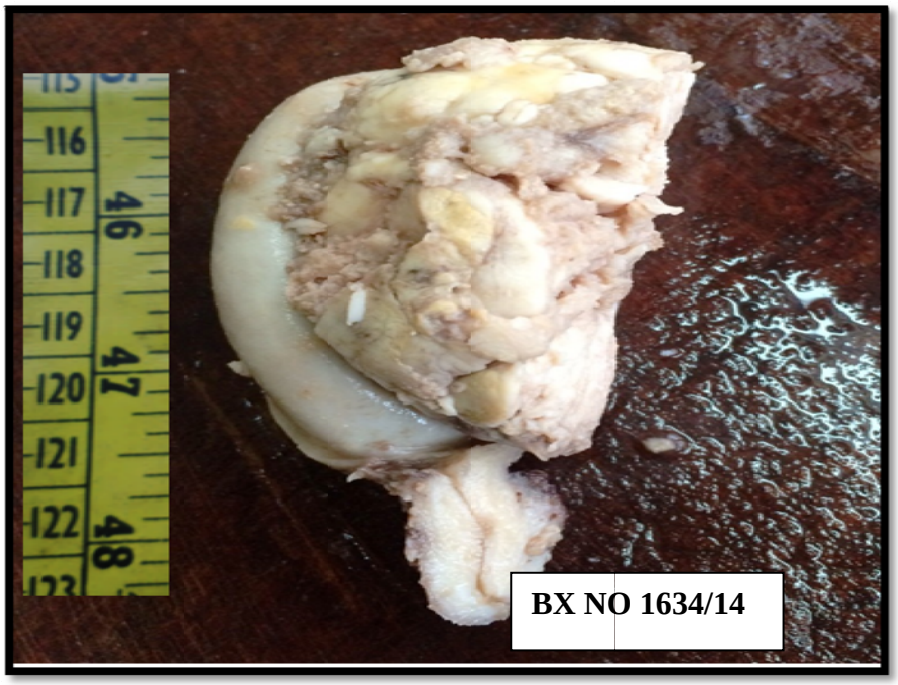


FIGURE: 3 - GROSS :Poorly differentiated endometrioid carcinoma of uterus presenting as a a proliferative growth.

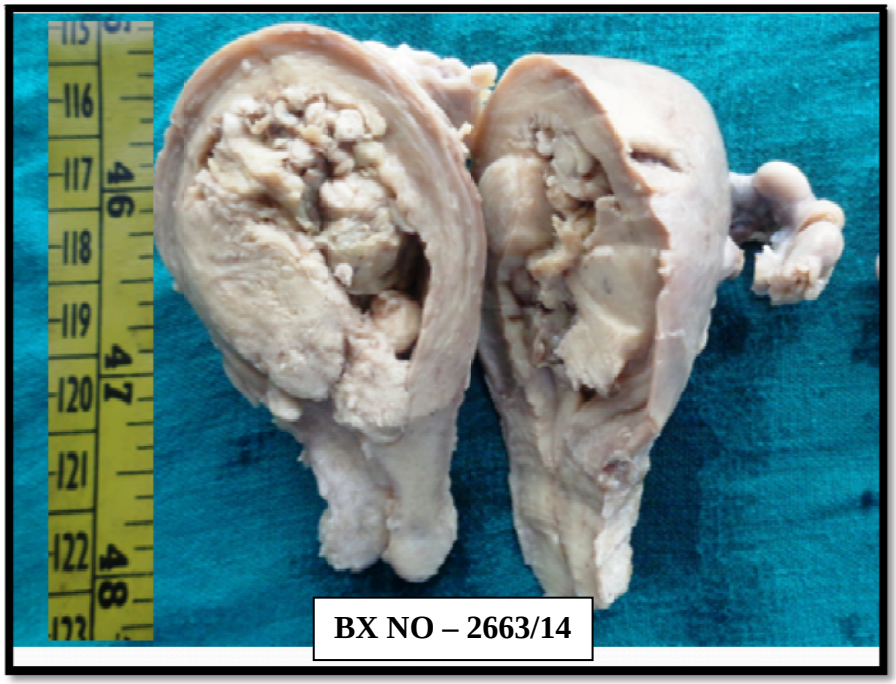


FIGURE: 4– GROSS – Clear cell carcinoma uterus presenting as a polypoidal growth.

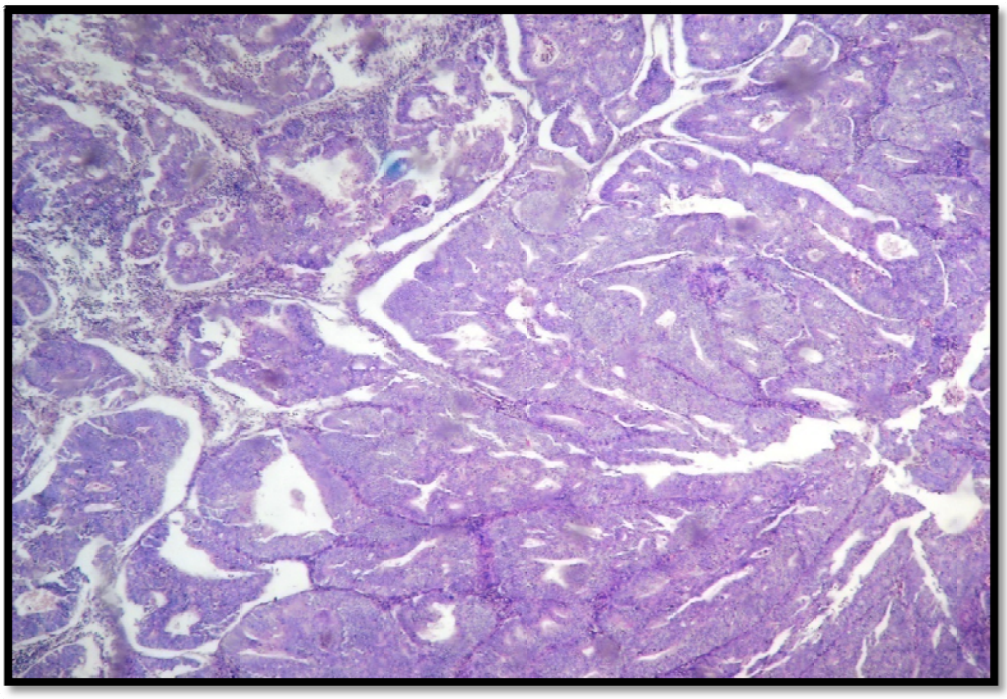


FIGURE :5 – well differentiated endometrioid adenocarcinoma of uterus - 100 X HPE NO – 1297/14.

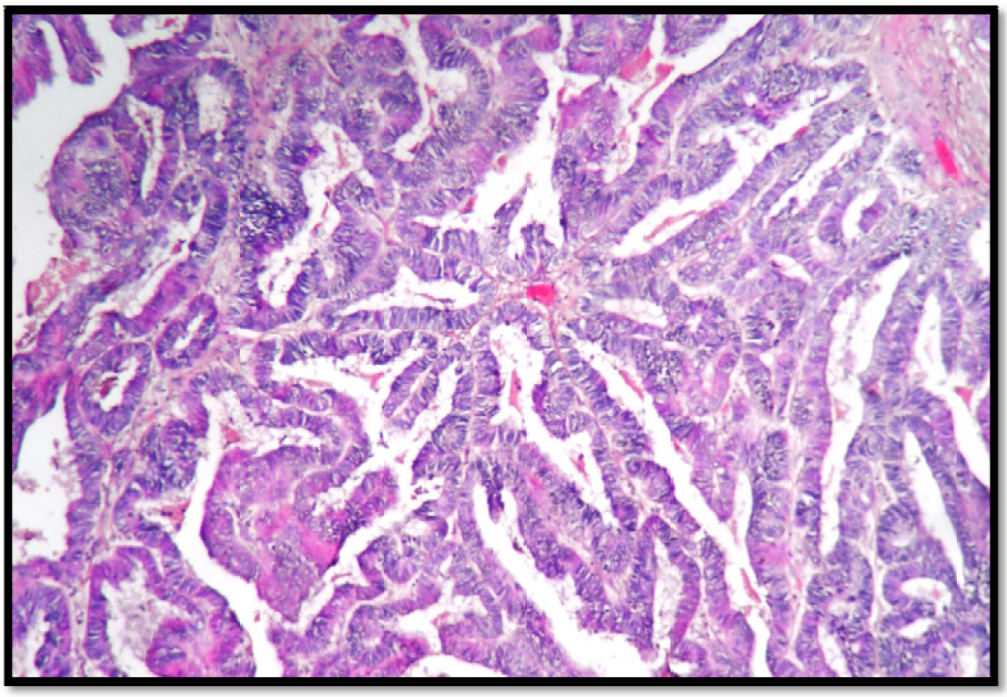


FIGURE : 6 – Villoglandular variant of endometrioid carcinoma 100X, HPE NO- 2855/12

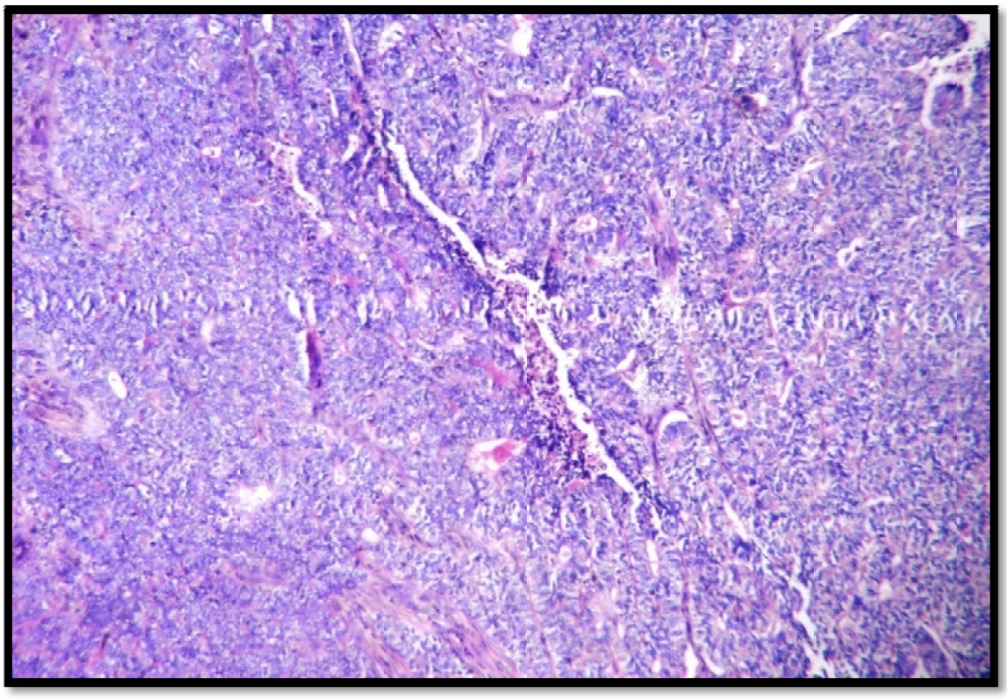


FIGURE 7: Moderately differentiated endometrioid adenocarcinoma, - 100X ; HPE NO – 2208/13.

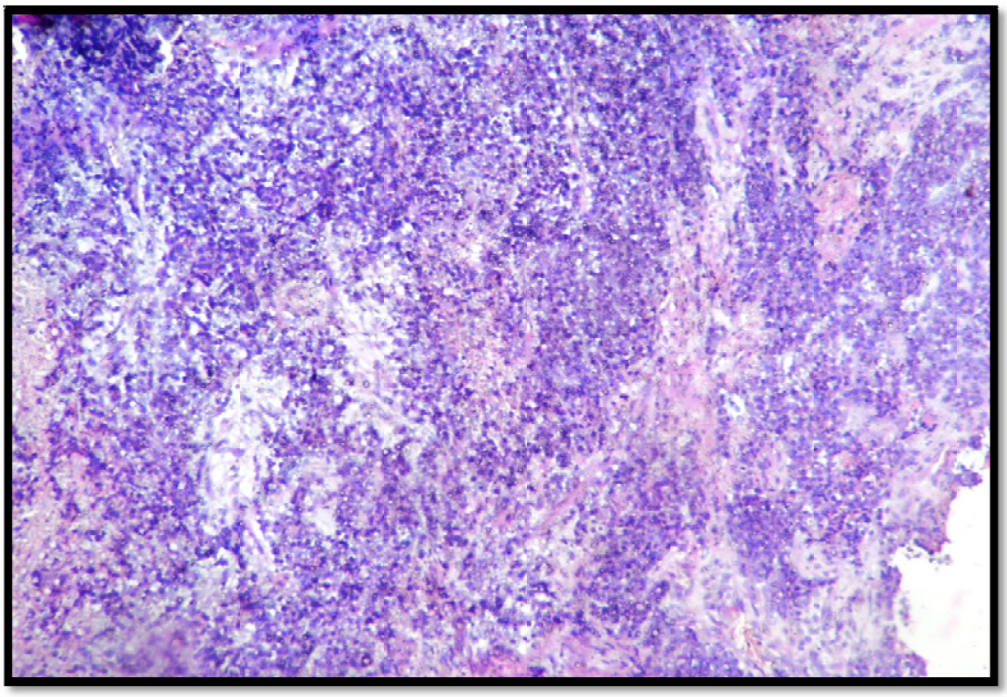


FIGURE 8: Poorly differentiated endometrioid adenocarcinoma – 100x ; HPE NO – 26/14 .

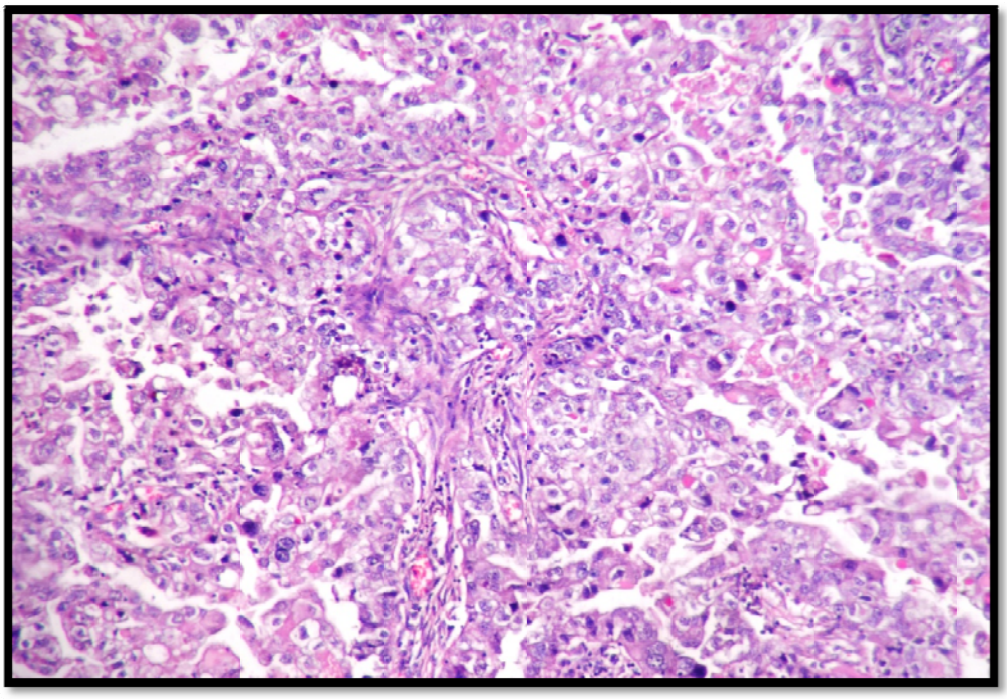


FIGURE 9: Clear cell carcinoma endometrium – 100X;HPE NO – 2663/14.

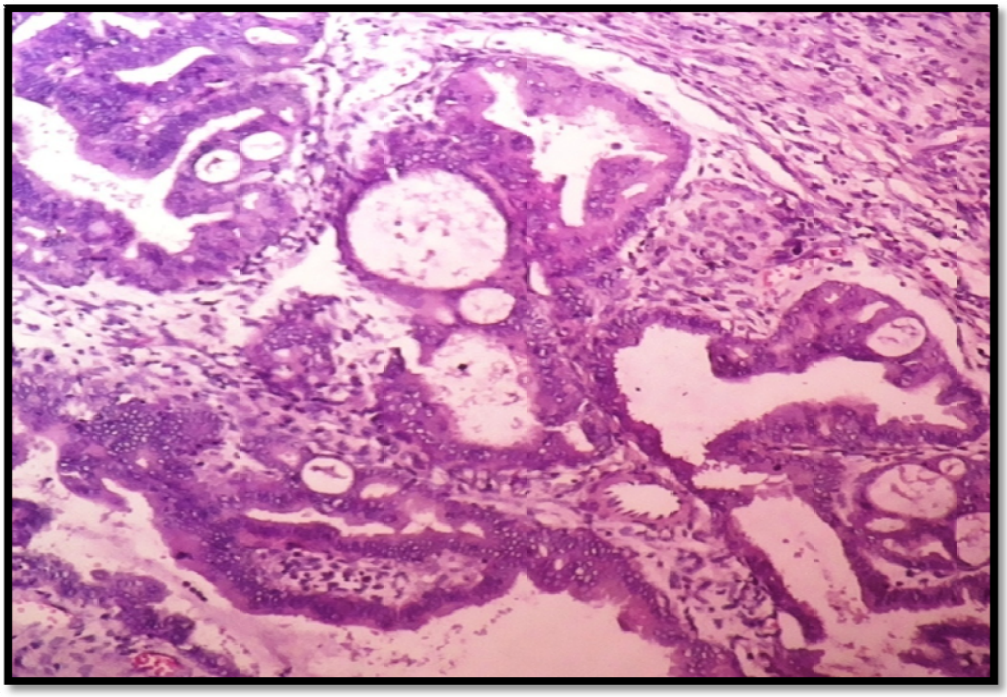


FIGURE 10: MMMT uterus-Adenocarcinoma component -400x;

HPE NO-2739/14

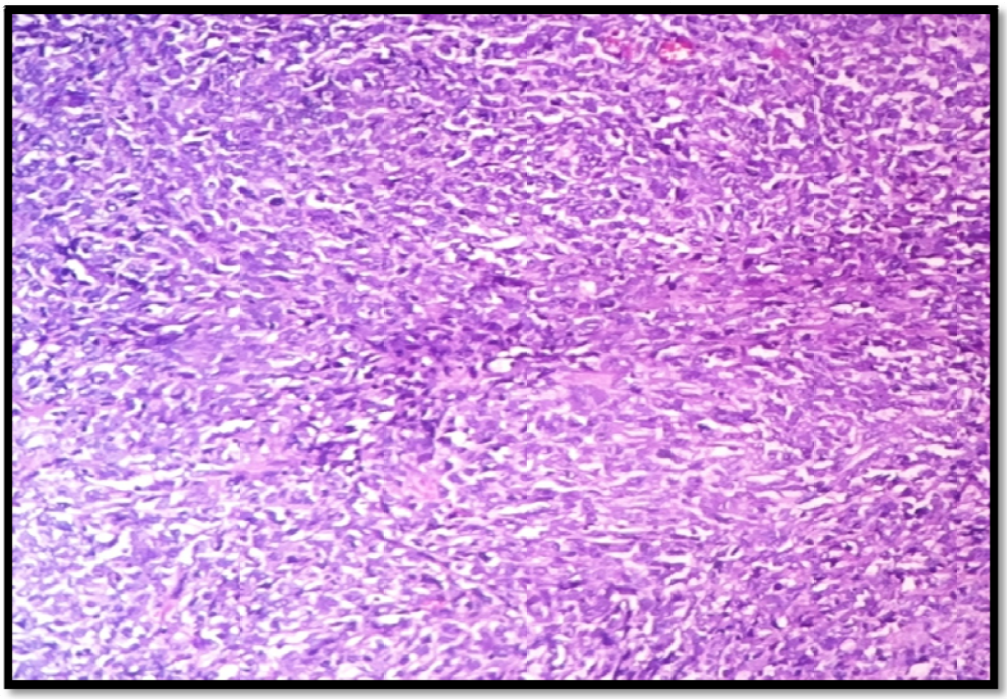


FIGURE 11:MMMT uterus – sarcomatous component;100x; HPE N0 – 2739/14.

TTF 1 EXPRESSION

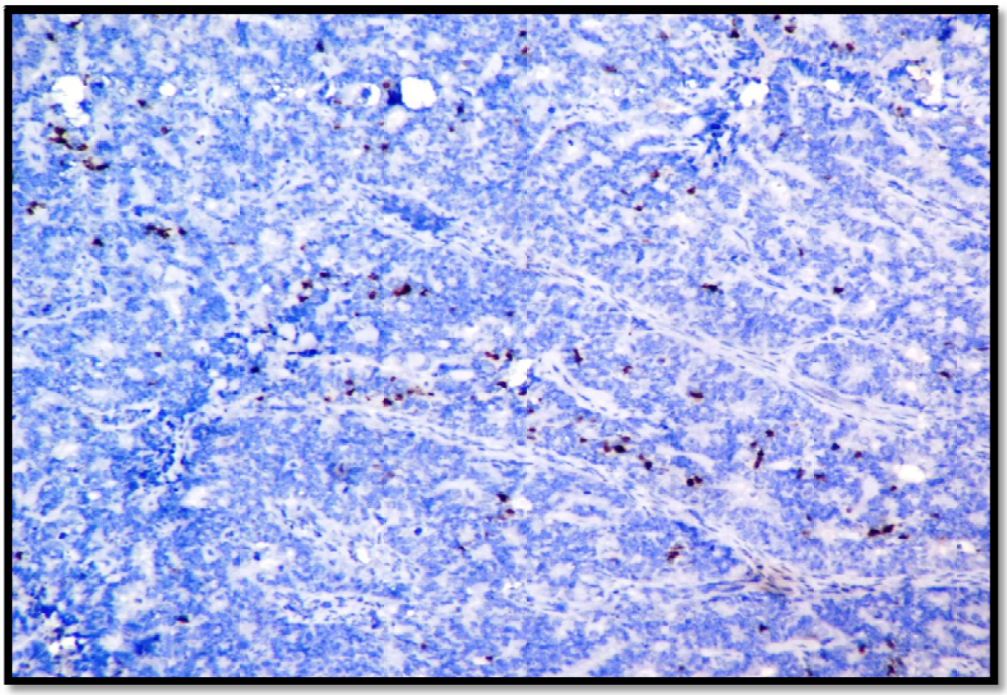


FIGURE 12 : 2208/14 - Focal nuclear positivity of TTF 1 in moderately differentiated endometrioid adenocarcinoma.

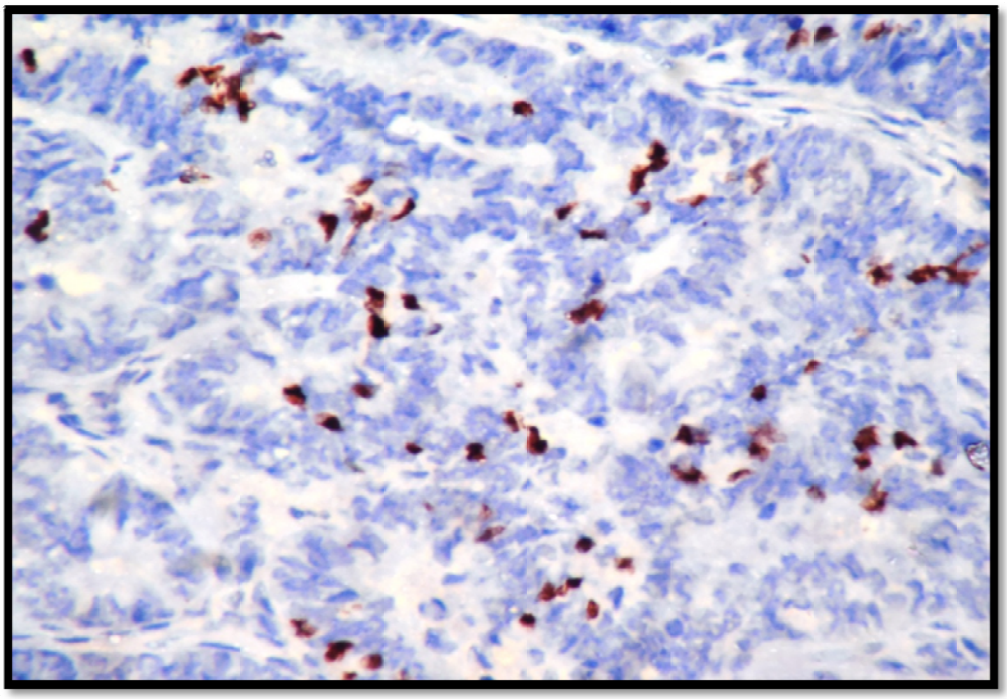


FIGURE 13: 2208/14- 400X – Focal nuclear positivity of TTF 1 in moderately differentiated endometrioid adenocarcinoma.

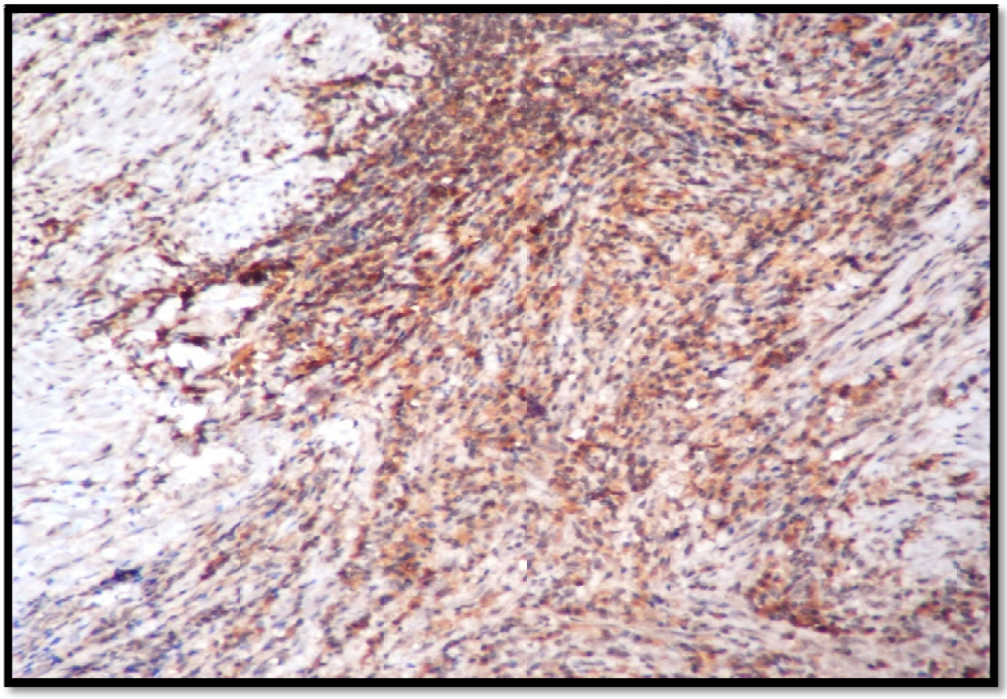


FIGURE 14: 26/14- Diffuse nuclear positivity of TTF 1 in poorly differentiated endometrioid adenocarcinoma.

DISCUSSION

DISCUSSION

Endometrial carcinoma is the common gynecological malignancy next to cervical and ovarian carcinoma.

This study is a prospective and retrospective study from January 2010 to December 2014 on endometrial carcinoma in the Institute of obstetrics and gynecology , madras medical college. A total of 93 cases were received in the hysterectomy specimens. Out of the 93 cases , well differentiated endometrioid carcinoma were 52,moderately differentiated endometrioid carcinoma were 15, poorly differentiated endometrioid carcinoma were 16 cases, serous carcinoma 1 case, clear cell carcinoma 3 cases, villoglandular carcinoma 1 case, undifferentiated carcinoma 1 case, MMMT 4cases.

Incidence :

Endometrioid carcinoma represents about 90% of the total cases in this study. This is in accordance with the study done by **Nirmala et al** [109] , in which endometrioid type constitutes 75 – 80 %.

Serous carcinoma incidence during these 5 years in this study is 1%, in literature its incidence is about 5 - 10 % and clear cell carcinoma incidence is 3%, in accordance with study done by **Nirmala et al**[109], where the incidence was between 3-5%.

MMMT incidence in this study is 4 % .According **Silverberg et al** [77], it's incidence is 5%.

Age group:

The age group affected most frequently in this study is 51 – 60 years with a age range of 20 to 80 years. Mean age is 54 years .Incidence of endometrial carcinoma in women aged below 40 years is 8.6% , in a study done by **Ota T et al** [110] where the incidence is between 2 to 14%.

The youngest age affected is 27 years in this study . In a study by **Farhi DC et al**[111] , the youngest age of women with endometrial carcinoma is 15 years.

Age group and histological type of endometrial carcinoma:

In this study , in women aged below 40 years ,most of them have low grade endometrioid carcinoma about 6.4% . In a study by **Garg K et al**[112] states that in women below 40 years low grade endometrioid carcinoma is common.

High grade endometrioid carcinomas, clear cell carcinoma ,serous carcinoma and MMMT occur in women above 40 years. This is similar to the

study done by **Hafezi S et al**[113], which states that elderly women have more incidence of high grade endometrial carcinoma.

Menstrual status:

In this 5 year study 93 cases of endometrial carcinoma , incidence in premenopausal women is 8.6 %, perimenopausal women is 37.6%, post menopausal women is 53.8%.So, the highest incidence rate is in postmenopausal women, this is in accordance to various studies in literature[114,115]. **Soliman et al** stated that endometrial carcinoma has mean age incidence of 61 years ,commonly in post menopausal women[116].

Parity:

In this study , most of the women with endometrial carcinoma are parous accounting for 82.8%, whereas nulliparous women has an incidence of 17.2%.

The literature states that nulliparous women have increased incidence of endometrial carcinoma. According to **Soliman et al**[116] incidence rate in nulliparous women was 54%.But in this study most were parous women.

Clinical features:

In this study 54% patients presented with postmenopausal bleeding ,45% with irregular bleeding pv,abdominal pain 11%,white discharge 4%,mass

descending pv 1 %.According **ESMO guidelines 2013**[1] the most common presenting symptoms is abnormal uterine bleeding accounting for more than 90% .

Gross:

In the 50 randomly selected cases the gross features were assessed, more than 90% have proliferative growth. Literature also states that most have exophytic appearance[117].

Histological types:

Conventional endometrioid adenocarcinoma constitutes about 90% in this study, with grade 1 carcinoma constituting about 63%, grade 2 constitutes 18% and grade 3 constitutes 19% . Literature states that about 50 % are well differentiated, 35 % are moderately differentiated and 15% poorly differentiated[112].But in this study moderately differentiated endometrioid carcinoma has a 1% higher incidence than poorly differentiated carcinoma.

The occurrence of clear cell carcinoma in this study is 3.2 %, in accordance to the study done by **Joyce varughese et al** [119]where the incidence is between 1% to 6%.

Abler et al [120] stated that the incidence of uterine serous carcinoma is 1%, in this study also only one case was reported accounting for 1.1%

In a study by **Silverberg et al** [121] the incidence of MMMT is around 5%, in this 5 year study also the incidence is about 4.3%.

Type of endometrial carcinoma:

The incidence of type 1 carcinoma during this 5 year period 2010 to 2014, is 73% and type 2 carcinoma is 27%.According to **Liu FS et al** [122], incidence of type 1 carcinoma is 70 to 80% and type 2 carcinoma is between 10 % to 20%.Thus the incidence stated in this study correlates with the literature studies.

FIGO staging:

Out of the 68 cases in stage I about 45 cases of well differentiated carcinoma accounting for 66% was reported ,moderately differentiated endometrioid carcinoma was 13%,poorly differentiated endometrioid carcinoma was 11%,MMMT was 4% , clear cell carcinoma was 1%.Thus majority of cases in stage I are low grade endometrioid carcinoma . **F.K.L Tournois et al**[132] in his study also has mentioned that most of women with endometrial carcinoma about 78.5% were diagnosed in stage I and most of them were grade 1 endometrioid carcinoma 41.3%, moderately differentiated endometrioid carcinoma 38%,poorly differentiated endometrioid carcinoma

20.7%.Thus in stage I most cases were well differentiated endometrioid carcinoma.

In stage II about 11 cases accounting for 11.8% of total cases were reported, majority were poorly differentiated endometrioid carcinoma 6 cases, 2 cases well differentiated carcinoma , 1 case each from clear cell carcinoma and MMMT . **F.K.L Tournois et al** [123] in his study reported 5.2% cases in stage II.

In stage III total of 12 cases were reported accounting for 13%.One case of undifferentiated carcinoma presented in stage IIIB. **F.K.L Tournois et al**[123] in his study reported about 11% cases in stage III. He has stated that incidence of grade 3 endometrioid carcinoma in stage III is higher but in this study no such association is found.

In stage IV B only one case (1.1%) of moderately differentiated endometrioid carcinoma was reported . **F.K.L Tournois et al** [123] reported 2.5% in stage IV.

TTF 1 expression in endometrial carcinoma:

In this study for 50 random cases including 30 cases of well differentiated endometrioid adenocarcinoma, none of them expressed positivity for TTF 1.

Out of the 8 cases of Moderately differentiated endometrioid carcinoma 2 cases showed focal positivity accounting for 25% and 75% were negative.

In a study by **Aaron ervine et al** [6]for 100 cases of low grade endometrioid carcinoma only 2 cases showed positivity ,one case showing diffuse positivity, other one showing focal positivity and 98% cases were negative.

In this study out of 38 cases, 2 cases of low grade endometrioid adenocarcinoma showed focal positivity for TTF 1 accounting for 5%. This is in concurrence with the study by **Aaron ervine et al** [6].

Out of 7 cases of poorly differentiated endometrioid carcinoma only one case showed diffuse positivity accounting for 14%.This is in concurrence with the study done by **Aaron et al** [6], where out of total 101 cases, 89% cases are negative, 7% cases are diffusely positive, 4% are focally positive.

In this study TTF 1 expression in clear cell carcinoma , out of 2 cases both are negative. This is in concurrence with the study by **Jaudah Al-Maghrabi et al** [7],where TTF 1 was negative for 2 cases for which the marker was done. But in another study Aaron et al , TTF 1 positivity was found in 2 cases out of 29 cases accounting for 7% .

For 3 cases of MMMT ,all were negative for TTF 1.But according to **Zhang et al** [124], TTF 1 expression present in 82% cases of MMMT.

TTF 1 and grade:

In this study expression of TTF 1 according to grade was studied. Out of 45 cases of endometrioid carcinoma, 2 cases of moderately endometrioid

carcinoma are positive and one case of poorly differentiated endometrioid carcinoma.

In study by **Ervine et al** [6] TTF 1 positivity of 2% in low grade endometrioid carcinoma and 11% in grade 3 endometrioid carcinoma.

But in this study only 2% showed diffuse TTF 1positivity and 4% showing focal TTF 1 positivity.

Deavers et al [125] showed that in a total of 32 cases of endometrioid carcinoma only 5 cases showed TTF 1 positivity accounting for 16%.

In this study out of 45 cases of endometrioid carcinoma, 3 cases showed positivity for TTF 1 accounting for 7 %.

The relationship between TTF 1 expression and grade of endometrioid carcinoma has a p value = 0.004, indicating that relationship is statistically significant in this study. Thus TTF 1 expression correlates with the grade of endometrioid carcinoma.

TTF 1 and Type of endometrial carcinoma:

In 50 randomly selected cases , 36 cases of type 1 , 2 cases showed focal positivity for TTF 1 with a percentage of 5.5% and in 11 cases of type 2 , one case was diffusely positive for TTF 1 with a percentage of 9%. On statistical assessment this association was not significant p value > 0.05.

TTF 1 and menstrual status:

In the 50 randomly selected cases, total of 6 cases in premenopausal women all were negative for TTF 1. In perimenopausal women total of 19 cases , one case of poorly differentiated showed diffuse positivity. In postmenopausal women total of 25 cases ,2 cases of moderately differentiated endometrioid carcinoma were focally positive for TTF1.

For a total 8 cases of moderately differentiated endometrioid carcinoma, 3 cases in premenopausal age group,2 cases in perimenopausal age group, 2 cases in postmenopausal age group. Two cases were focally positive for TTF 1 in the postmenopausal women whereas it was negative in other 2 menstrual statuses.

In poorly differentiated endometrioid carcinoma only one case out of the 7 cases was positive. It was positive in perimenopausal women.

Thus the association of TTF 1 positivity with the menstrual status of women in this study is that positivity in moderately differentiated endometrioid carcinoma occurs in postmenopausal women.

On statistical analysis p value = 0.453, showing that association of TTF 1 positivity with menstrual status of women is not statistically significant.

TTF 1 and stage:

In this study out of the three positive cases for TTF 1 ,for one case staging was done as the specimen was received in fragments and the other two low grade endometrioid carcinoma ,one case was in stage IA and other was in stage IB. **Aaron ervine et al** [6] in his study also reported 2 positive cases in low grade endometrioid carcinoma in the stage mentioned above.

In the 5 year study of endometrioid carcinoma, 3 cases (2-MMMT,1-clear cell carcinoma with a percentage of 67% MMMT ,33% clear cell carcinoma) had carcinoma breast .For one case of MMMT the women was a known case of carcinoma breast diagnosed before 8 years and for other 2 cases carcinoma breast was diagnosed synchronously along with carcinoma endometrium .

But **Ashley Sinclair et al** [126] in their study reported carcinoma breast in 16% MMMT and 14% in clear cell carcinoma.

For the 50 randomly selected cases , follow up details were collected , 12 cases follow up details were not available. All the other cases were treated according to their stage of presentation by surgery , chemotherapy and radiotherapy. Cases were followed up for a mean duration of 14 months . In cases that were positive for TTF 1 , 2 cases lost follow up and one case of low grade grade endometrioid carcinoma in stage IB postsurgery , radiotherapy was given and she is followed for 7 months and there is no adverse

behaviour till now when compared to other low grade endometrioid carcinoma that were negative for TTF 1.

According to the study done by **Aaron et al** [6],TTF 1 positivity in low grade endometrioid carcinoma is associated with poor prognosis but in this study out of the 2 positive cases of low grade endometrioid carcinoma ,follow up could not be traced for one and other case was followed for 7 months and no difference in survival was noted , so comment on the prognosis can be made only on long term follow up.

SUMMARY

SUMMARY

Among 17032 biopsies that were received in the Institute of obstetrics and gynecology ,Madras medical college 93 cases of endometrial carcinoma were reported during the 5 year period from January 2010 to December 2014.

In 93 cases 52 cases (55.9%) were well differentiated endometrioid carcinoma, 15 cases (16%) were moderately carcinoma,16 cases(17%) were poorly differentiated carcinoma, 1 case (1%) of villoglandular carcinoma,1 case (1%) of serous carcinoma,3 cases(3.2%) of clear cell carcinoma,4 cases (4.3%) of MMMT , 1 case (1%) of undifferentiated carcinoma .Thus in our study the incidence of well differentiated endometrioid carcinoma is higher than other histological types.

The peak age group incidence of endometrial carcinoma in our study is 51 to 60 years accounting for 34.4% where as incidence in women below 30 years is 1.1% and incidence in women above 60 years is 27%.

Most of the endometrial carcinoma in women below 40 years in our study were low grade with a percentage of 6.4%.

High grade endometrioid carcinoma,clear cell carcinoma,serous carcinoma and MMMT occurred in women above 40 years in this study.

Incidence of endometrial carcinoma in postmenopausal women is 53.8% in our study.

The percentage of endometrial carcinoma in parous women is 83% and in nulliparus women is 17%.

In our study the incidence of Type 1 carcinoma is 73% and Type 2 carcinoma is 27% .Most of the low grade carcinoma presented in stage I in this study.

Among 50 randomly selected cases TTF 1 marker was done ,only 3 cases showed positivity for TTF 1. Two cases of moderately differentiated endometrioid carcinoma were focally positive and one case of poorly differentiated carcinoma was diffusely positive for TTF 1 ,all others were negative.

The relationship between TTF 1 positivity and grade of endometrioid carcinoma has a p value of 0.004 which is statistically significant.

On correlating TTF 1 positivity with stage, out of 3 positive cases 2 cases were in stage IA and IB ,for the other positive case staging was not done.

CONCLUSION

CONCLUSION

In our study the incidence of different types of endometrial carcinoma in the 5 years from January 2010 to December 2014 was studied.

The aim of our study was to study the expression of TTF 1in endometrial carcinoma and also to study its positivity according to grade of endometrial carcinoma.

In this study, total of 3 cases of endometrial carcinoma was positive and the relationship between TTF 1 positivity with grade of endometrial carcinoma was significant though majority of cases of endometrial carcinoma were negative for TTF 1.

Thus this study confirms that TTF 1 positivity correlates with grade of endometrial carcinoma. Out of the 3 positive cases ,the follow up for 7 months was available for only case of stage I low grade endometrioid carcinoma and the comment on prognosis can only be made on long term follow up.

ANNEXURE I

WHO histological classification of tumours of the uterine corpus

Epithelial tumours and related lesions

Endometrial carcinoma

Endometrioid adenocarcinoma

Variant with squamous differentiation

Villoglandular variant

Secretory variant

Ciliated cell variant

Mucinous adenocarcinoma

Serous adenocarcinoma

Clear cell adenocarcinoma

Mixed cell adenocarcinoma

Squamous cell carcinoma

Transitional cell carcinoma

Small cell carcinoma

Undifferentiated carcinoma

Others

Endometrial hyperplasia

Nonatypical hyperplasia

Simple

Complex

Atypical hyperplasia

Simple

Complex

Endometrial polyp

Tamoxifen related lesions

Mesenchymal tumours

Endometrial stromal tumours

Endometrial stromal sarcoma

Endometrial stromal nodule

Undifferentiated sarcoma

Smooth muscle tumours

Leiomyosarcoma

Epithelioid variant

Myxoid variant

Smooth muscle tumour of

uncertain malignant potential

Leiomyoma, NOS

Mitotically active

Cellular variant

Hemorrhagic cellular

Epithelioid variant

Myxoid

Atypical variant

Lipoleiomyoma

Diffuse leiomyomatosis

Dissecting leiomyoma

Intravenous leiomyoma

Metastasizing leiomyoma

Miscellaneous mesenchymal tumours

Mixed endometrial stromal and smooth muscle tumour

Perivascular epithelioid cell tumour

Adenomatoid tumour

Other malignant mesenchymal tumours

Other benign mesenchymal tumours

Mixed epithelial and mesenchymal tumours

Carcinosarcoma

Adenosarcoma

Carcinofibroma

Adenofibroma

Adenomyoma

Gestational trophoblastic disease

Trophoblastic neoplasms

- Choriocarcinoma
- Placental site trophoblastic tumour
- Epithelioid trophoblastic tumour

Molar pregnancies

Non neoplastic,non molar trophoblastic lesions

- Placental site nodule and plaque
- Exaggerated placental site

Miscellaneous tumours

Sex cord like tumours

Neuroectodermal tumours

Tumors of germ cell type

Melanotic paraganglioma

Lymphoid & haematopoeitic

Malignant lymphoma

Leukaemia

Secondary tumours

ANNEXURE II

FIGO STAGING (2009):

IA	Tumor limited to the inner half of myometrium
IB	Tumor invasion into the outer half of myometrium
II	Tumor invades cervical stroma
IIIA	Tumor invades serosa and/or adnexa
IIIB	Vaginal and/or parametrial involvement
IIIC1	Metastases to pelvic lymph nodes
IIIC2	Metastases to paraaortic lymph nodes
IVA	Tumor invasion of bladder and/or bowel mucosa
IVB	Distant metastases including intraabdominal and/or inguinal lymph nodes

ANNEXURE III

Immunohistochemistry procedure:

Slide Preparation:

1. Sections with a thickness of 4 μ were cut from formalin fixed paraffin embedded tissue samples and transferred to gelatin-chrome alum coated slides.
2. The slides were incubated for overnight at 58ºC.
3. The sections were deparaffinised in xylene for 15 minutes x 2 changes.
4. The sections were dehydrated with absolute alcohol for 5 minutes for 2 changes.
5. Then the sections were washed with tap water for 10 minutes.
6. The slides are then immersed in distilled water upto 5 minutes.

Antigen Retrieval:

1. Heat induced antigen retrieval was done with microwave oven in appropriate temperature with appropriate buffer for 20 minutes. This step unmasks the antigenic determinants of fixed tissue sections.
2. The slides were then cooled to room temperature for 20 minutes and washed with tap water for 5 minutes.
3. The slides were then rinsed with distilled water for 5 minutes.
4. then the slides were washed with appropriate wash buffer (phosphate buffer) for 5 minutes x 2 changes.
5. Peroxidase block was then applied for 10 minutes.
6. The slides then were washed in phosphate buffer for 5 minutes x 2 changes.
7. Sections were covered with protein block for 5 minutes.

Antibody application:

1. The sections were drained (without washing) and appropriate primary antibody is applied and incubated for 30 minutes.
2. The slides were washed in the phosphate buffer for 5 minutes x 2 changes.
3. The slides were covered with Primary antibody amplifier for 10 minutes.
4. The slides were washed in the phosphate buffer for 5 minutes x 2 changes.
5. The slides were covered with HRP micropolymer Quanto for 10 minutes.
6. The slides were washed in the phosphate buffer for 5 minutes x 2 changes.

Chromogen application:

1. DAB substrate was prepared by diluting 1 drop of DAB Quanto chromogen to 1 ml of DAB Quanto buffer.
2. DAB substrate solution was applied on the sections for 5 minutes.
3. Wash the slides then in distilled water for 2 minutes.
4. counterstain the section with Hematoxylin for 2 seconds.
5. Wash the slides in running tap water for 5 minutes.
6. Air dry the slides, cleared with xylene and mounted with DPX.

Alternate methods of antigen retrieval

- Pressure cooker antigen retrieval
- Microwave and trypsin antigen retrieval

ANNEXURE IV

PROFORMA

Name	:	
Age	:	
IP Number	:	
Biopsy No	:	
Presenting symptoms	:	post-menopausal bleeding/white discharge/abdominal pain
Parity	:	parous/nulliparous
Menstrual status	:	menstruating/ post-menopausal
Ultrasound findings	:	
CT findings	:	
Clinical diagnosis	:	
Fractional curettage	:	
Type of specimen	:	hysterectomy
Gross	:	proliferative/infiltrative
Microscopy	:	Histological diagnosis according to WHO classification
IHC (TTF 1 expression)	:	negative/ focal/diffuse

ANNEXURE V

INFORMATION SHEET

Title : A study of expression of Thyroid transcription factor(TTF- 1) in endometrial adenocarcinoma of uterine corpus

- Your specimen has been accepted.
- We are conducting a study on Uterine endometrial adeno carcinoma among patients attending Institute of Obstetrics & Gynaecology, Hospital, Chennai and for that your specimen may be valuable to us.
- The purpose of this study is to diagnose the expression of a special marker (TTF-1) in uterine endometrial adenocarcinoma.
- We are selecting certain cases and if your specimen is found eligible, we may be using your specimen to perform extra tests and special studies which in any way do not affect your final report or management.
- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.
- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.
- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator Signature of participant

Date:

ஆராய்ச்சி தகவல் தாள்

ஆராய்ச்சி தலைப்பு : **கர்பப்பை புற்றுநோயில் சிறப்பு குறியீடு (TTF1) தன்மையை கண்டறிதல்.**

ஆய்வாளர் : மரு. **M.** பிருந்தா

நோய்குறியியல் துறை,

சென்னை மருத்துவக் கல்லூரி,

சென்னை - 600003.

தங்களது கர்பப்பை புற்றுநோய் கட்டி (அறுவை சிகிச்சை செய்யப்பட்ட கட்டி) இங்கு பெற்றுக் கொள்ளப்பட்டது.

சென்னை மகப்பேறு மற்றும் மகளிர் நோயியல் நிலையம் மருத்துவமனைக்கு வரும் நோயாளிகளிடம் இருக்கும் கர்பப்பை புற்றுநோய் கட்டிகளைப் பற்றிய ஒரு ஆராய்ச்சி இங்கு நடைபெற்று வருகின்றது.

கர்பப்பை புற்றுநோய் கட்டியில் சிறப்பு குறியீடு **(TTF1)** செய்து அதன் தன்மையை கண்டறிந்து ஆராய முடியும் என்பதே இந்த ஆராய்ச்சியின் நோக்கமாகும்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் உங்களுடைய திசுக்களை எடுத்து சில சிறப்புப் பரிசோதனைக்கு உட்படுத்தி அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்புக்குள்ளாகாது என்பதையும் தெரிவித்துக் கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியில் இருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்புப் பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆய்வை பற்றிய சந்தேகங்களுக்கு தொடர்பு கொள்ள வேண்டியவர் :
மரு. **M.**பிருந்தா. செல் : 9488382773

பங்கேற்பாளர் கையொப்பம்..... இடம் :..... தேதி :.....

பங்கேற்பாளர் பெயர் மற்றும் விலாசம் .....

ஆராய்ச்சியாளர் கையொப்பம்..... இடம் :..... தேதி :.....

INFORMED CONSENT FORM

Title of the study **: A STUDY OF EXPRESSION OF THYROID TRANSCRIPTION FACTOR (TTF1) IN**

ENDOMETRIAL ADENOCARCINOMA OF UTERUS.

Name of the Participant:

Name of the Principal (Co-Investigator) :

Name of the Institution : Institute of obstetrics and gynaecology, Madras Medical College.

Name and address of the sponsor / agency (ies) (if any) :

Documentation of the informed consent

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in "**A STUDY OF EXPRESSION OF THYROID TRANSCRIPTION FACTOR IN ENDOMETRIAL ADENO-CARCINOMA OF UTERINE CORPUS"**

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study in which the resected endometrial tumors will be subjected to immunohistochemistry and histopathological examination.
4. I have been explained about my rights and responsibilities by the investigator. I have the right to withdraw from the study at any time.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past _____ months including any native (alternative) treatment.
6. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
7. I have understand that my identity will be kept confidential if my data are publicly presented
8. I have had my questions answered to my satisfaction.
9. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

For adult participants:

Name and signature / thumb impression of the participant (or legal representative if participant

incompetent)

Name _____ Signature_____
Date_____

Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____
Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____
Date_____

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு : **கர்பப்பை புற்றுநோயில் சிறப்பு குறியீடு (TTF1) தன்மையை கண்டறிதல்.**

சென்னை மருத்துவக் கல்லூரி நோய்குறியியல் துறையில் பயிலும் முதுகலை மருத்துவர் M. பிருந்தா, அவர்கள் மேற்கொள்ளும் இந்த ஆய்வில் பங்குகொள்ள ..... ஆகிய நான் முழு மனதுடன் சம்மதிக்கிறேன்.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு நான் எனது சம்மதத்தைத் தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்ப்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் தான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியிலிருந்து எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

நான் கர்பப்பை புற்றுநோய் கட்டி நோய்கள் குறித்த இந்த ஆராய்ச்சியின் விவரங்களைக் கொண்ட தகவல் தாளைப் பெற்றுக் கொண்டேன்.

நான் என்னுடைய சுயநினைவுடன் மற்றும் முழு சுதந்திரத்துடன் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக் கொள்ள சம்மதிக்கிறேன்.

எனக்கு அறுவை சிகிச்சை செய்யப்பட்டு நோய்க்குறியியல் துறையில் சதைப் பரிசோதனைக்கு பயன்பட்ட மெழுகுக்கட்டிகளை வைத்து ஆராய்ச்சி மற்றும் சிறப்புப் பரிசோதனை செய்யது கொள்ள சம்மதம் தெரிவிக்கிறேன்.

பங்கேற்பாளர் கையொப்பம்..... இடம் :..... தேதி :.....

பங்கேற்பாளர் பெயர் மற்றும் விலாசம் .....

ஆராய்ச்சியாளர் கையொப்பம்..... இடம் :..... தேதி :.....

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MASTER CHART

MASTER CHART - I

S.NO	BX.NO	AGE	P/NP	menstrual status	C.F	F.C	STA. LAP	GRADE	FIGO STAGE	TYPE
1	412/10	59	P	3	1	Anaplastic	Undiff ca	NA	IIIB	2
2	474/10	40	P	1	2	Well diff	Well diff	1	IA	1
3	620/10	50	P	2	2,3	Well diff	Well diff	1	IIIA	1
4	671/10	62	P	3	1	Poor diff	Poor diff	3	IB	2
5	724/10	62	P	3	1	Well diff	Well diff	1	IB	1
6	797/10	70	P	3	1	Clear ca	Clear ca	NA	IB	2
7	844/10	63	NP	3	1	Well diff	Well diff	1	IB	1
8	1193/10	50	P	2	2,4	Poor diff	Poor diff	3	II	2
9	1302/10	78	NP	3	1	Poor diff	Poor diff	3	IIIA	2
10	2412/10	52	P	2	2	Mod diff	Mod diff	2	IIIC1	1
11	2535/10	65	P	3	1	Well diff	Well diff	1	II	1
12	2581/10	45	NP	2	2	Well diff	Well diff	1	IA	1
13	2621/10	45	P	2	2	Well diff	Well diff	1	IA	1
14	2767/10	63	P	3	1	Mod diff	Mod diff	2	IIIC2	1
15	2845/10	48	NP	2	2	Well diff	Well diff	1	IA	1
16	3103/10	56	P	3	1	Mod diff	Mod diff	2	IA	1
17	3048/10	50	P	2	2	Mod diff	Mod diff	2	IA	1
18	58/11	50	P	2	2	Well diff	Mod diff	2	IA	1
19	326/11	55	NP	3	1	Serous ca	Serous ca	NA	IB	2
20	428/11	56	NP	3	1	Well diff	Well diff	1	IIIA	1
21	550/11	70	P	3	1	Mod diff	Mod diff	1	IB	1
22	1049/11	60	P	3	1	Well diff	Well diff	1	IA	1

23	1250/11	34	NP	1	2	Well diff	Well diff	1	IA	1
24	1559/11	65	P	3	1,3	MMMT	MMMT	NA	IA	2
25	2055/11	50	P	2	2	Poor diff	Poor diff	3	II	2
26	2254/11	61	P	3	1	Well diff	Well diff	1	IA	1
27	2288/11	60	P	3	1	Mod diff	Poor diff	3	II	2
28	2289/11	53	P	2	2	Mod diff	Poor diff	3	IB	2
29	2358/11	58	P	3	1	Well diff	Well diff	1	IB	1
30	2638/11	68	P	3	1	Well diff	Well diff	1	IA	1
31	2730/11	46	P	2	2	Well diff	Well diff	1	IA	1
32	2969/11	41	P	2	2	Well diff	Well diff	1	IA	1
33	3168/11	52	P	2	2	Well diff	Well diff	1	IA	1
34	3211/11	57	P	3	1	Well diff	Well diff	1	IB	1
35	3339/11	67	P	3	1	Well diff	Mod diff	2	IB	1
36	3461/11	57	NP	3	1	Well diff	Well diff	1	IA	1
37	17/12	70	P	3	1	Well diff	Well diff	1	IB	1
38	46/12	57	P	3	1,4	Well diff	Well diff	1	IA	1
39	349/12	45	P	2	2	Well diff	Well diff	1	IA	1
40	1463/12	40	P	1	2	Well diff	Mod diff	2	IIIC1	1
41	2198/12	55	P	3	1	Well diff	Well diff	1	IA	1
42	2268/12	70	P	3	1	Well diff	Well diff	1	IA	1
43	2388/12	55	P	3	1	Well diff	Well diff	1	IB	1
44	2400/12	45	P	2	2,4	Well diff	Well diff	1	IA	1
45	2522/12	56	NP	3	1	Poor diff	Poor diff	3	IB	2
46	2547/12	60	P	3	1	Well diff	Well diff	1	IIIA	1
47	2558/12	48	P	2	2,3	not done	MMMT	NA	IA	2

48	2597/12	60	P	3	1	Well diff	Well diff	1	IA	1
49	2606/12	45	NP	2	2	Mod diff	Mod diff	2	IVB	1
50	2855/12	57	P	3	1	VG ca	VG ca	1	IA	1
51	3086/12	48	P	2	2	Well diff	Well diff	1	IIIC2	1
52	SP16/13	61	P	3	1	Well diff	Well diff	1	IA	1
53	SP33/13	57	NP	3	1	Poor diff	Poor diff	3	IB	2
54	SP36/13	59	P	3	1	Well diff	Well diff	1	IA	1
55	414/13	52	P	2	2	Well diff	Well diff	1	II	1
56	660/13	46	P	2	2	Well diff	Well diff	1	IA	1
57	684/13	54	P	2	2	Well diff	Well diff	1	IB	1
58	1417/13	62	P	2	2	Well diff	Well diff	1	IB	1
59	1678/13	45	P	2	2	Well diff	Well diff	1	IB	1
60	2025/13	37	P	1	2,3	Mod diff	Mod diff	2	II	1
61	2113/13	36	P	1	2	Well diff	Well diff	1	IA	1
62	2208/13	65	P	3	1	Well diff	Mod diff	2	IA	1
63	2219/13	45	P	2	2	Well diff	Well diff	1	IB	1
64	2677/13	42	P	2	2	Poor diff	Poor diff	3	II	2
65	2813/13	40	P	1	2	Poor diff	Poor diff	3	IA	2
66	SP26/14	50	NP	2	1,3	Undiff ca	Poor diff	3	not done	2
67	63/14	57	P	3	1	Well diff	Well diff	1	IA	1
68	77/14	62	P	3	1	Well diff	Well diff	1	IB	1
69	239/14	55	P	3	1	Well diff	Well diff	1	IB	1
70	545/14	50	P	2	2	Undiff ca	Poor diff	3	IA	2
71	639/14	48	P	2	2	not done	Poor diff	3	II	2
72	671/14	55	NP	3	1	MMMT	MMMT	NA	II	2

73	790/14	55	P	3	1,3	Well diff	Well diff	1	IA	1
74	864/14	65	NP	3	1	Well diff	Well diff	1	IB	1
75	888/14	65	NP	3	1,3	Well diff	Well diff	1	IB	1
76	899/14	48	P	2	2	Mod diff	Mod diff	2	IB	1
77	987/14	60	P	3	1,3	Well diff	Mod diff	2	IIIA	1
78	1200/14	50	P	2	2,3	Well diff	Well diff	1	IIIA	1
79	1297/14	63	P	3	1	Well diff	Well diff	1	IA	1
80	1569/14	50	P	2	2,3,4	Clear ca	Clear ca	NA	II	2
81	1634/14	40	P	1	2	Poor diff	Poor diff	3	II	2
82	1670/14	47	P	2	2	Well diff	Well diff	1	IA	1
83	1798/14	42	P	2	2	Well diff	Well diff	1	IB	1
84	2032/14	62	P	3	5	not done	Well diff	1	IA	1
85	2158/14	65	P	3	1	Mod diff	Mod diff	2	IB	1
86	2186/14	65	P	3	1	Poor diff	Poor diff	3	IA	2
87	2663/14	65	P	3	1	Clear ca	Clear ca	NA	IIIA	2
88	2739/14	54	P	2	2	MMMT	MMMT	NA	IA	2
89	2838/14	60	P	3	1	Well diff	Well diff	1	IA	1
90	2873/14	58	P	3	1	Poor diff	Poor diff	3	IA	2
91	3081/14	41	P	2	2	Comp hyp	Well diff	1	IA	1
92	3168/14	27	NP	1	2	Mod diff	Mod diff	2	IA	1
93	3175/14	56	P	3	1	Well diff	Well diff	1	IA	1

KEY TO MASTER CHART I

P	-	parous
NP	-	nulliparous
F.C	-	fractional curettage

Menstrual status:

1	-	premenopausal
2	-	perimenopausal
3	-	postmenopausal

C.F- clinical features:

1	-	postmenopausal bleeding
2	-	bleeding pv
3	-	abdominal pain
4	-	white discharge
5	-	mass descending per vagina
Ca	-	carcinoma
Mod	-	moderate
Undiff	-	undifferentiated
Comp hyp	-	complex hyperplasia with atypia
NA	-	Not applicable

MASTER CHART - II

S.NO	BX.NO	AGE/SEX	P/NP	menstrual status	CF	FC	GROSS	HPE	GRADE	FIGO STAGE	TYPE	TTF1	Tt&FOLLOWUP
1	17/12	70	P	3	1	Well diff	1	Well diff	1	IB	1	neg	RT;24 mnths
2	349/12	45	NP	2	2	Well diff	1	Well diff	1	IA	1	neg	12 mnths
3	1463/12	40	P	1	2	Well diff	2	Mod diff	2	IIIC1	1	neg	RT, chemo;11 mnths
4	2198/12	55	P	3	1	Well diff	1	Well diff	1	IA	1	neg	26 mnths
5	2268/12	70	P	3	1	Well diff	1	Well diff	1	IA	1	neg	16 mnths
6	2388/12	55	P	3	1	Well diff	1	Well diff	1	IB	1	neg	RT;16 mnths
7	2522/12	56	NP	3	1	Poor diff	1	Poor diff	3	IB	2	neg	RT;26 mnths
8	2547/12	60	P	3	1	Well diff	1	Well diff	1	IIIA	1	neg	-
9	2558/12	48	P	2	2,3	MMMT	1	MMMT	NA	IA	2	neg	-
10	2597/12	60	P	3	1	Well diff	1	Well diff	1	IA	1	neg	21 mnths
11	2606/12	45	NP	2	2	Mod diff	2	Mod diff	2	IVB	1	neg	chemo; 5 mnths
12	2855/12	57	P	3	1	Well diff	1	Well diff	1	IA	1	neg	28 mnths
13	3086/12	48	P	2	2	Well diff	2	Well diff	1	IIIC2	1	neg	-
14	SP16/13	61	P	3	1	Well diff	1	Well diff	1	IA	1	neg	12 mnths
15	SP36/13	59	P	3	1	Well diff	1	Well diff	1	IA	1	neg	-
16	414/13	52	P	2	2	Well diff	1	Well diff	1	II	1	neg	RT chemo;24 mnths
17	660/13	46	P	2	2	Well diff	1	Well diff	1	IA	1	neg	-
18	684/13	54	P	2	2	Well diff	1	Well diff	1	IB	1	neg	RT;10 mnths
19	1678/13	45	P	2	2	Well diff	1	Well diff	1	IIIA	1	neg	RT chemo
20	2025/13	37	P	1	2,3	Mod diff	1	Mod diff	2	II	1	neg	RT
21	2113/13	36	P	1	2	Well diff	1	Well diff	1	IA	1	neg	-
22	2208/13	65	P	3	1	Well diff	1	Mod diff	2	IA	1	focal	-
23	2219/13	45	P	2	2	Well diff	1	Well diff	1	IB	1	neg	RT;10 mnths
24	2677/13	42	P	2	2	Poor diff	1	Poor diff	3	II	2	neg	RT

25	2813/13	40	P	1	2	Poor diff	1	Poor diff	3	IA	2	neg	RT
26	SP26/14	50	NP	2	2,3	Undiff ca	1	Poor diff	3	-	2	diffuse	-
27	63/14	57	P	3	1	Well diff	1	Well diff	1	IA	1	neg	12 mnths
28	77/14	62	P	3	1	Well diff	1	Well diff	1	IB	1	neg	-
29	639/14	48	P	2	2	not done	2	Poor diff	3	II	2	neg	RT
30	671/14	55	NP	3	1	MMMT	1	MMMT	NA	II	2	neg	k/c/o ca breast ,RT
31	790/14	55	P	3	1,3	Well diff	1	Well diff	1	IA	1	neg	13 mnths
32	864/14	65	NP	3	1	Well diff	1	Well diff	1	IB	1	neg	RT
33	888/14	65	NP	3	1,3	Well diff	1	Well diff	1	IB	1	neg	RT; 5 mnths
34	899/14	48	P	2	2	Mod diff	1	Mod diff	2	IB	1	neg	RT;15 mnths
35	987/14	60	P	3	1,3	Well diff	1	Mod diff	2	IIIA	1	neg	RT chemo;10 mnths
36	1200/14	50	P	2	2,3	Well diff	1	Well diff	1	IIIA	1	neg	RT chemo
37	1297/14	63	P	3	1	Well diff	1	Well diff	1	IA	1	neg	15 mnths
38	1569/14	50	P	2	2,3,4	Clear ca	1	Clear ca	NA	II	2	neg	RT;10 mnths
39	1634/14	40	P	1	2	Poor diff	1	Poor diff	3	II	2	neg	RT ;6 mnths
40	1670/14	47	P	2	2	Well diff	1	Well diff	1	IA	1	neg	6 mnths
41	1798/14	42	P	2	2	Well diff	1	Well diff	1	IB	1	neg	RT
42	2032/14	62	P	3	5	not done	1	Well diff	1	IA	1	neg	6 mnths
43	2158/14	65	P	3	1	Mod diff	1	Mod diff	2	IB	1	focal	RT; 7 mnths
44	2663/14	65	P	3	1	Clear ca	1	Clear ca	NA	IIIA	2	neg	ca breast, RT
45	2739/14	54	P	2	2	MMMT	1	MMMT	NA	IA	2	neg	ca breast, RT
46	2838/14	60	P	3	1	Well diff	2	Well diff	1	IA	1	neg	-
47	2873/14	58	P	3	1	Poor diff	1	Poor diff	3	IA	2	neg	6 mnths
48	3081/14	41	P	2	2	Comp hyp	1	Well diff	1	IA	1	neg	-
49	3168/14	27	NP	1	2	Mod diff	1	Mod diff	2	IA	1	neg	-
50	3175/14	56	P	3	1	Well diff	1	Well diff	1	IA	1	neg	4 mnths

KEY TO MASTER CHART 2

P – parous

NP- nulliparous

F.C – fractional curettage

Menstrual status:

1 - premenopausal

2 - perimenopausal

3 - postmenopausal

C.F- clinical features

1 - postmenopausal bleeding

2 - bleeding pv

3 - abdominal pain

4 - white discharge

5 - mass descending per vagina

Gross :

1 - Proliferative growth

2 - Infiltrative growth

Ca - carcinoma

Mod - moderate

Undiff	-	undifferentiated
Com hyp	-	complex hyperplasia with atypia
RT	-	radiotherapy
Chemo	-	chemotherapy
Mnths	-	months

TTF 1 :

Neg	-	Negative
Focal	-	less than 50% positive
Diffuse	-	more than 50% positive